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The issue of stereochemical control in multicomponent reactions and glycosylation processes.

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ABSTRACT

Multicomponent reactions (MCRs) are processes that show high atom and step economy; two different parts of my thesis were linked by MCRs.

In the first part, levulinic acid was converted into a variety of bicyclic nitrogen heterocycles passing by an Ugi reaction. The obtained intermediate was then converted in the final product *via* a simple S_N2 cyclization.

The second part, instead, was dedicated to the obtainment of organo-catalysts structurally based on secondary and tertiary amine groups. First attempts, to get the latter in bicyclic structures, involved a starting MCR with L-prolinol, but the reaction showed low diastereoselectivity and the cyclization failed. A different strategy was aimed to obtain secondary amines and resulted to be more efficient. The involvement of a seven-membered cyclic imine, with a chiral center in C-3, in a Ugi-Joullié reaction resulted in a very diastereoselective process. Using a silyl oxy derived carboxylic acid, an Ugi adduct with a protected alcohol is obtained. Thus, an intramolecular cyclization can be performed producing the final free amine group. The obtained amine was used to perform the first catalysis tests in Michael and aldol reactions. Although no catalytic activity was detected, different reaction conditions and structures have still to been tested.

Finally, the reaction mechanism in self-promoted glycosylations was investigated. They involve a trichloroacetimidate as glycosyl donor which is activated by an acceptor that contains an acid sulfonamide portion. An alcoholic function was added to the acceptor with a consecutive possible production of both *O*- and *N*-glycosides. Dissociative mechanism favors the first while an associative mechanism brings to the second. The study showed the chemoselectivity and, to some extent, the stereoselectivity of the reaction to be controlled by tuning the parameters *e.g.* the polarity of the solvent, the concentration of donor and acceptor and the use of additives such as lithium salts.

CONTENTS

1. INTRODUCTION

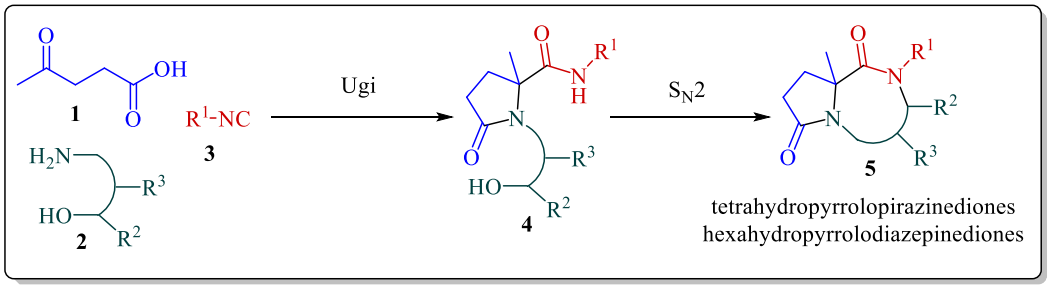
My doctorate thesis has been devoted to three different projects, correlated only in part. Therefore, both the thesis and this introduction have been divided into three parts. The use of multicomponent reactions for a fast and diversity-oriented synthesis and the use of aminoalcohols or their derivatives in stereoselective synthesis are the main aspects in common among these three different parts.

1.1 Use of biobased levulinic acid for a fast and efficient construction of bicyclic heterocycles

Levulinic acid **1** (Scheme 1) is one of the most important building blocks derived for biomass.[1] It is quoted in the list of 12 most important lignocellulosic-derived compounds.[2] It can be easily obtained by acid treatment of hexoses.[3] Production of levulinic acid on large scale is already a well assessed methodology. Its price is, at the moment, about 1 $/kg, but it is expected to go further down, using waste sugar sources. Thus, the main problem now is not how to get it, but how to valorize it. Some applications in the polymer field are under study.[4] Far less investigated are transformations into nitrogen derivatives.[5]

The goal was to exploit multicomponent reactions, in particular the isocyanide-based Ugi reaction, in order to convert levulinic acid into a variety of bicyclic heterocycles **5** (Scheme 1). The other key substrates for this approach are aminoalcohols **2**, that are often obtainable as well from renewable sources, and can be accessed in a huge variety, including chiral ones. The strategy involves just two steps, namely an Ugi reaction followed by a Mitsunobu-type cyclization.

A brief State-of-the-Art of multicomponent reactions (MCRs), including the Ugi reaction, and of the power of combining MCRs with post-MCR cyclizations is reported in chapter 2.1.



Scheme 1. Proposed strategy to convert levulinic acid into bicyclic heterocycles.

As thoroughly described in chapter 2.2, the approach turned out to be successful. We have indeed been able to synthesize the target bicyclic heterocycles in high overall yields, and with great operational simplicity. When using chiral aminoalcohols, the multicomponent reaction showed very low or no diastereoselectivity, but both diastereomers could be easily converted to the final product. After optimization of the second cyclization both six- and seven-membered rings were obtained.

1.2 Multicomponent synthesis of chiral amines to be exploited as new enantioselective organocatalysts

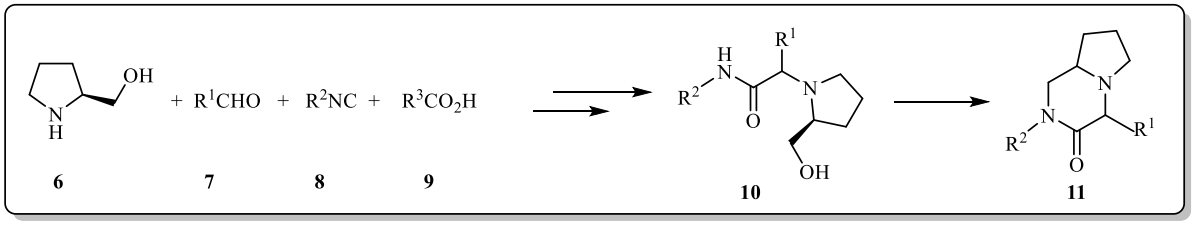
Multicomponent synthesis of chiral amines and their evaluation as new potential enantioselective organocatalysts represented the main part of my thesis.

Organocatalysis is a relatively new research area that has witnessed a dramatic growth in the last 20 years, since the pioneering work of Barbas and List in 2000.[6] Among organocatalysts, tertiary and secondary amines play a paramount role. The former can be used for general basic catalysis or, after conversion to quaternary salts, as phase-transfer catalysts.[7,8] The latter are even more important, since they can be involved in both enamine and iminium ion catalysis.[9]

In most cases, the organocatalysts employed thus far are obtained by derivatization of natural chiral amines or aminoacids. For example, proline and its derivatives are definitely the most popular in this area.[6,10] Also *Cinchona* alkaloids have been often used.[7] However, this limits the exploration of chemical diversity to the derivatives easily obtainable starting from this "chiral pool" members.

Multicomponent reactions are very well suited for the exploration of chemical diversity, since they allow to introduce at least 3 diversity inputs in a single step, and, for this reason, they have been extensively employed in the synthesis of libraries of potential drug candidates.[11] Thus, during my thesis I followed two different approaches, thoroughly described in chapter 2.3, to exploit this kind of reactions for the synthesis of new potential organocatalysts.

The first one was based on previous reports by Sheppard *et al*., and was aimed to tertiary amines derived from prolinol **6** or functionalized prolinols (Scheme 2).[12,13] Reaction of these secondary aminoalcohols under Ugi conditions should lead to a deviation of the normal reactivity, affording β-aminoamides **10**, instead of β-acylaminoamides, which are the typical Ugi products. These tertiary amines could be rigidified by cyclizations that exploit the alcoholic moiety.

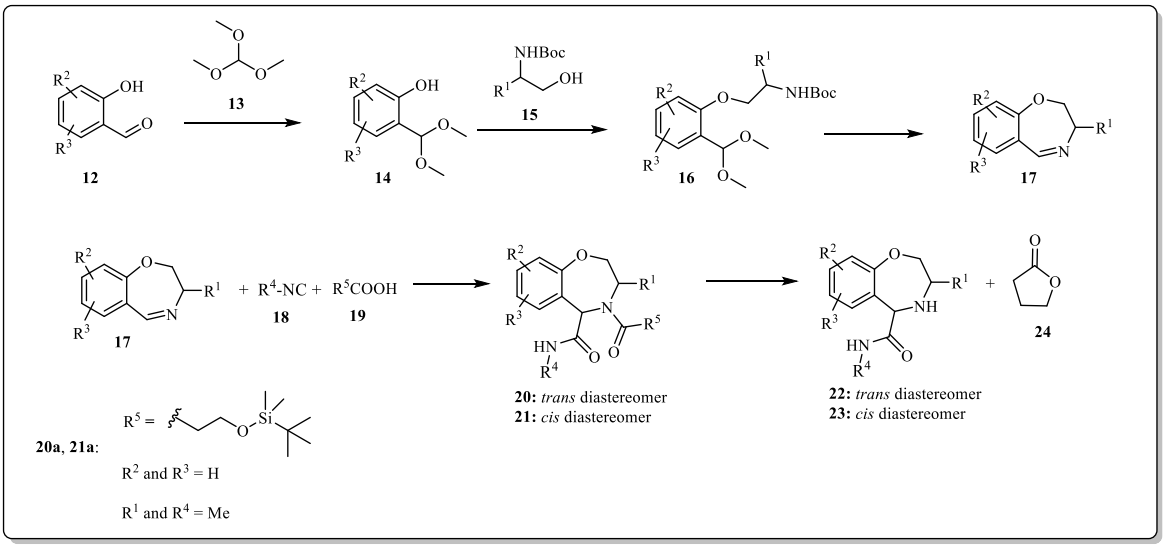


Scheme 2. Proposed synthetic path to obtain bicyclic compounds having tertiary amine groups.

This approach proved to be problematic since the multicomponent reaction showed low yields and diastereoselectivity. Furthermore, the two diastereomers resulted difficult to separate and first attempts towards cyclization failed. Although we believe that probably, with further efforts, these drawbacks could be overcome; we preferred to move to the second strategy described in Scheme 3, which was aimed to the synthesis of secondary amines.

Such approach was based on the synthetic strategy used by my research group for the synthesis of tetrahydrobenzoxazepines which exploits Ugi-Joullié reaction as multicomponent process.[14] Boc-aminoalchols **15**, obtained from α-Boc-amino-acids, were chosen as starting

materials in order to have a greater availability of substrates and to increase the steric induction of the final potential catalyst. The multicomponent reaction showed a very high diasteroselectivity as will be reported and the two diastereomers could be easily separated through a simple chromatographic column. The conversion of the amide to the amine group was not so trivial. The Ugi-Joullié product **20-21** showed, indeed, a great sensitivity to basic conditions, used into an attempt to hydrolyze the amide group, bringing an epimerization phenomenon. Post-MCR cyclization turned out to be useful for the scope. By insertion of a protected alcohol into the multicomponent adduct, an intramolecular cyclization can be performed after remotion of the protecting group. Thus, **20a** and **21a** can be converted into the desired products **22** and **23** under the appropriate conditions (Scheme 3).



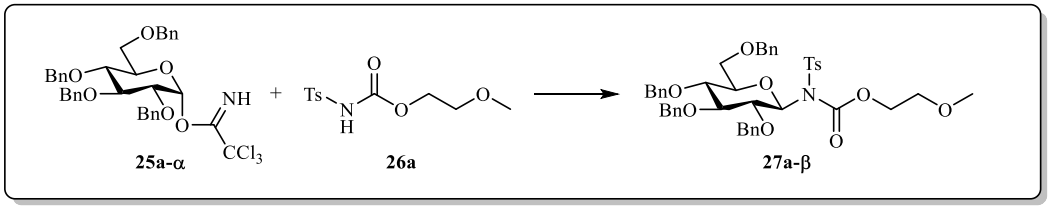
Scheme 3. Proposed synthetic path to obtain bicyclic compounds having secondary amine groups.

The obtained amine (chapter 2.3) offered a chance to perform the first tests to study the catalytic activity of these compounds. Michael and aldol reactions were chosen with this purpose. Many reaction conditions have been tested, but unfortunately, no catalytic activity has been observed so far.

1.3 Mechanistic studies of self-promoted glycosylations

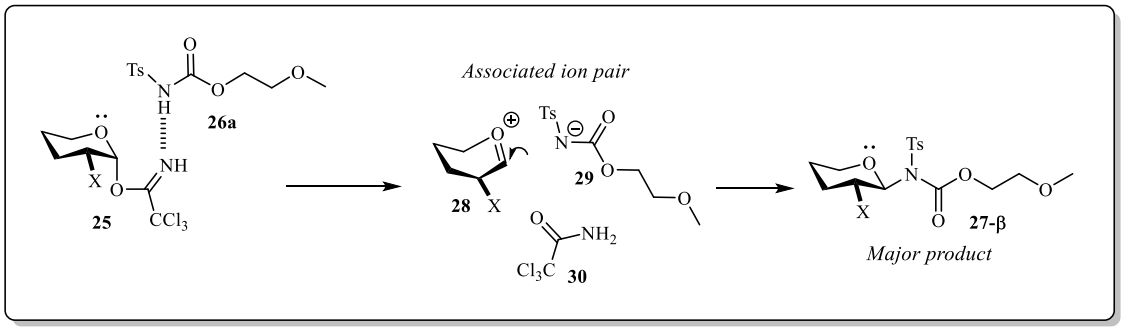
Finally, during my Erasmus project (chapter 3), in the laboratories of Prof. Pedersen in Copenhagen, I studied the reaction mechanism in self-promoted glycosylations,[15] and how it is influenced by the reaction conditions.

Previously, Prof. Pedersen has developed a new and efficient strategy to perform self-promoted *N*-glycosylation (Scheme 4).[15]



Scheme 4. Self-promoted *N*-glycosylation.

Self-promoted reactions are processes that can be activated by one of the involved reagents without using external catalysts or additives.[16,17] The acidity of the sulfonamide functionality makes the glycosyl acceptor **26a** able to activate the trichloroacetimidate (TCA) donors **25** with a subsequent nucleophilic attack to the glycosyl cation **28** *i.e.* it acts as both catalyst and nucleophile (Scheme 5).

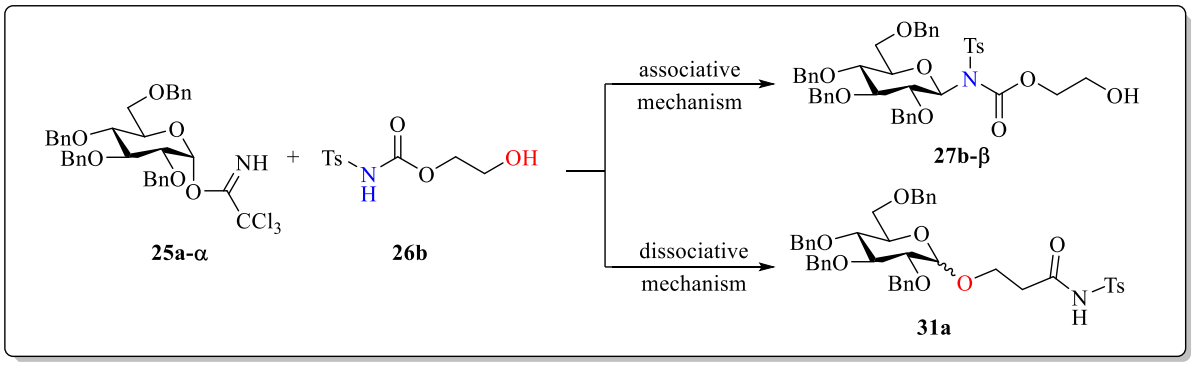


Scheme 5. Putative mechanism of self-promoted *N*-glycosylation.

Associated ion pairs were proposed as favorite for the reaction mechanism starting from axial-TCA donors. Contact and solvent-separated ion pairs are on the borderline between a S_N1 and a S_N2 mechanism. Small changes in the reaction condition can therefore shift the balance to either site. Important parameters in this are *e.g.* the polarity of the solvent and its ability to promote a charge separation.[18-20] The dissociative reaction path allows two competing reaction pathways resulting in low anomeric selectivity.

To better understand the mechanism and the solvent influence on the self-promoted reaction, an alcoholic function was inserted in the acceptor (Scheme 6). The nucleophilic attack from this group would be favored only by the formation of dissociated ion pairs. On the other side *N*-glycosylation is favored with a more associative mechanism. Thus, simply valuing the *N*-glycoside: *O*-glycoside ratio it is possible to understand the favored mechanism involved in the reaction.

As chiral compounds are produced, all these reactions have been studied also from a stereochemical point of view.



Scheme 6. *N*- vs *O*-glycosylation in self-promoted processes.

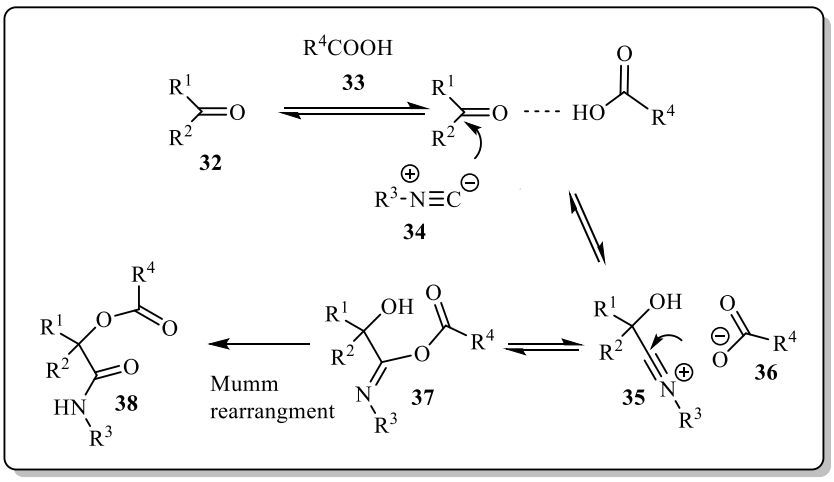
The study showed the chemoselectivity and, to some extent, the stereoselectivity of the reaction to be controlled by tuning the parameters *e.g.* the polarity of the solvent, the concentration of donor and acceptor and using additives like lithium salts.

2. RESULTS AND DISCUSSION

2.1 Multicomponent reactions

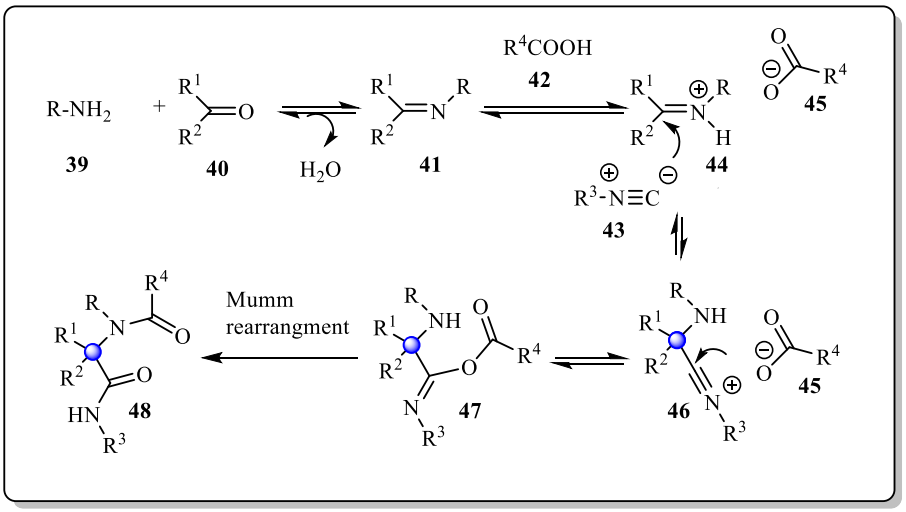
Multicomponent reactions (MCRs) are defined as processes where three or more substrates are combined in a single step, to give a product which contains all the essential portions of the used species.[21] Thus, based on the structure of the starting materials many products with different molecular complexity can be obtained with high step and atom economy making MCRs a sustainable strategy for the synthesis of highly diverse compound libraries. Furthermore, the scaffold of the products with new chirality centers makes them suited for exploring biological targets and drug-like entities.

Two of the most famous multicomponent processes are the Passerini and Ugi reactions. The first, introduced by the italian Mario Passerini in 1921 consists in the synthesis of an α-acyloxycarboxamide by simply mixing a carbonylic compound, an isocyanide and a carboxylic acid.[22] The activation of the carbonyl group by the acid allows the isocyanide to give rise to a nucleophilic attack to produce intermediate **37** (Scheme 7). An acyl migration (Mumm rearrangement) completes the reaction mechanism to generate the final product.



Scheme 7. Mechanism of Passerini reaction.

The one introduced by Ugi in 1959 adds the preformation of an imine, by interaction between a carbonylic compound and an amine, in the reaction mechanism (Scheme 8).[23] Isocyanides are suitable substrates for this kind of reactions being able to react with both electrophiles and nucleophiles at the same atom to form α-adducts. These species can be available in commercial form, but also many procedures, like the use of diphosgene and *in situ* reactions with Burgess reagent, have been proposed for their synthesis.[24,25] The Ugi reaction occurs thanks to protonation of the pre-formed imine **41** by the weak acid followed by nucleophilic attack by the isocyanide **43** to the iminium ion **44**. The resulting nitrilium ion **46** is then attacked by the carboxylate ion **45** and the Mumm rearrangement completes the reaction to form the final β-acylaminoamides (Scheme 8).



Scheme 8. Mechanism of Ugi reaction.

As a new stereogenic center is created, stereochemical issues have be considered. If at least one reagent is chiral two different diastereomers will indeed be formed. However, when using chiral isocyanides, amines, carboxylic acids, or carbonyl compounds as the chirality inductive components, no respectable level of diastereoselectivity is achieved and most of α-chiral isocyanides or α-chiral aldehydes undergo a racemization under the Ugi reaction conditions.[26]

Different strategies have been developed to discover novel MCRs. Some of them are presented in this thesis.

2.2 Synthesis of bicyclic compounds starting from levulinic acid

A very effective strategy to increase scaffold diversity without developing new MCRs is the combination of existing MCRs with complexity-generating reactions. If a nucleophilic group is inserted in the multicomponent product, an intramolecular cyclization would be possible. This so-called post-MCR cyclization strategy (Figure 1) has been used in many works to achieve significant variation of the resulting 4-MCR scaffolds and some of them involve levulinic acid **1** (Scheme 9).

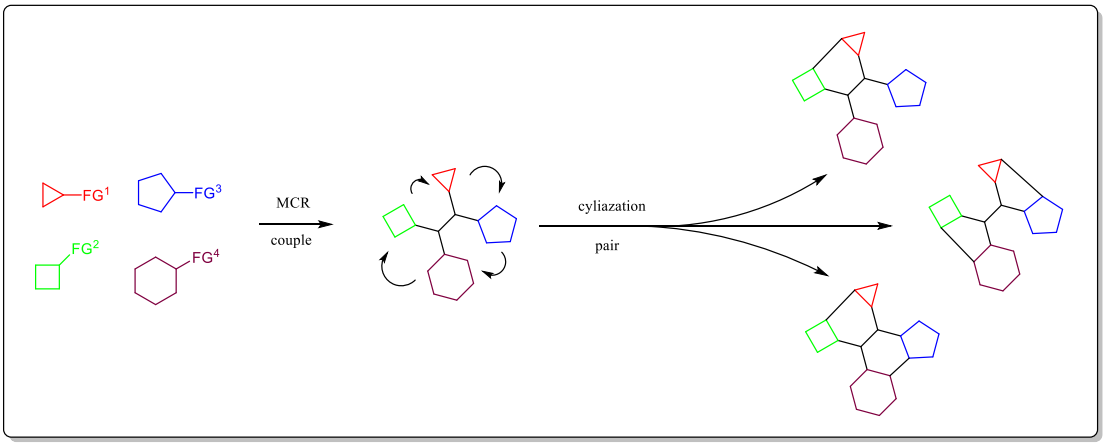
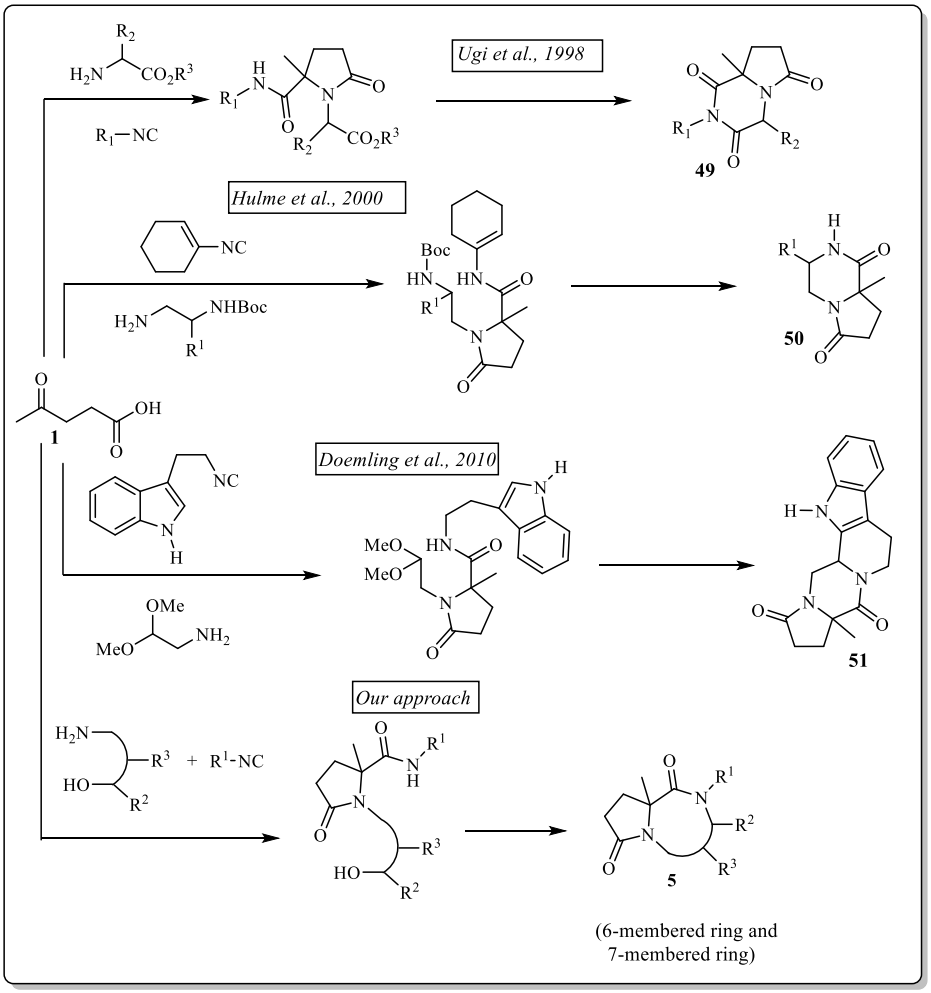


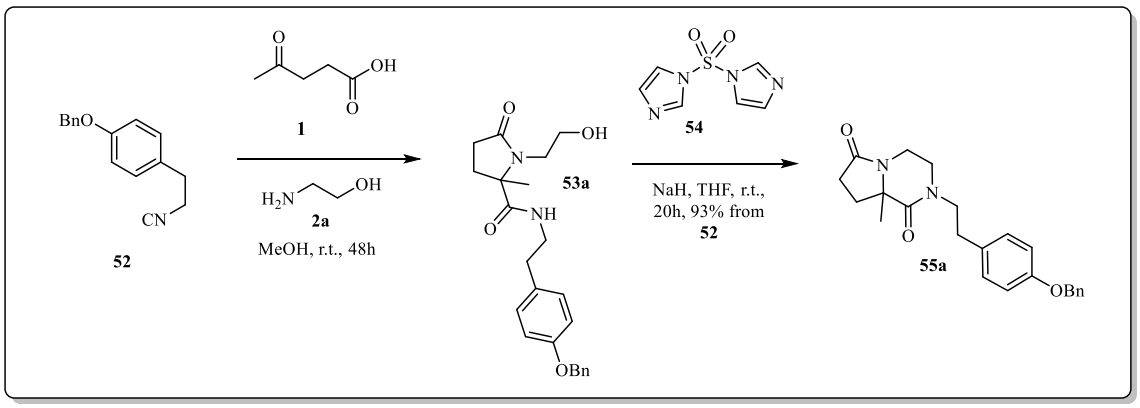
Figure 1. The generation of scaffold diversity by combining MCRs with cyclization reactions according to the build/couple/pair strategy.

It has been used, for example, by Ugi *et al.* to obtain compounds **49**, but they are imides, and thus less interesting for their hydrolytical instability.[27] On the other hand, ketopiperazines **50** and **51**, synthesized by Hulme and Doemling respectively, are limited from the point of view of the introduction of diversity: in **50** the isocyanide group is lost upon cyclization,[28] whereas the synthesis of **41** necessarily requires an indole containing isocyanide.[29] Our approach, depicted in Scheme 9, seemed more flexible and diversity-oriented. Based on the thorough experience of our group,[30-32] and of other authors,[33-36] in Ugi reactions followed by intramolecular aliphatic substitutions, we planned to employ amino alcohols as one of the two additional components in the Ugi reactions with levulinic acid **1**. Then, the isocyanide derived secondary amide group can react with the alcoholic function through a Mitsunobu or Mitsunobu-like reaction to produce a cyclization process. Two of the three components could be modified and different sizes of the diazalactam **5** can be achieved by varying the length of the spacer between the amino and the hydroxy groups. An added advantage of this strategy is that several amino alcohols may be obtained from biomass as well, including chiral enantiopure ones. The products of this two-step approach are quite uncommon bicyclic systems that join two "privileged structures":[37-39] the pyrrolidinone[40] and the piperazine[41] or diazepine.



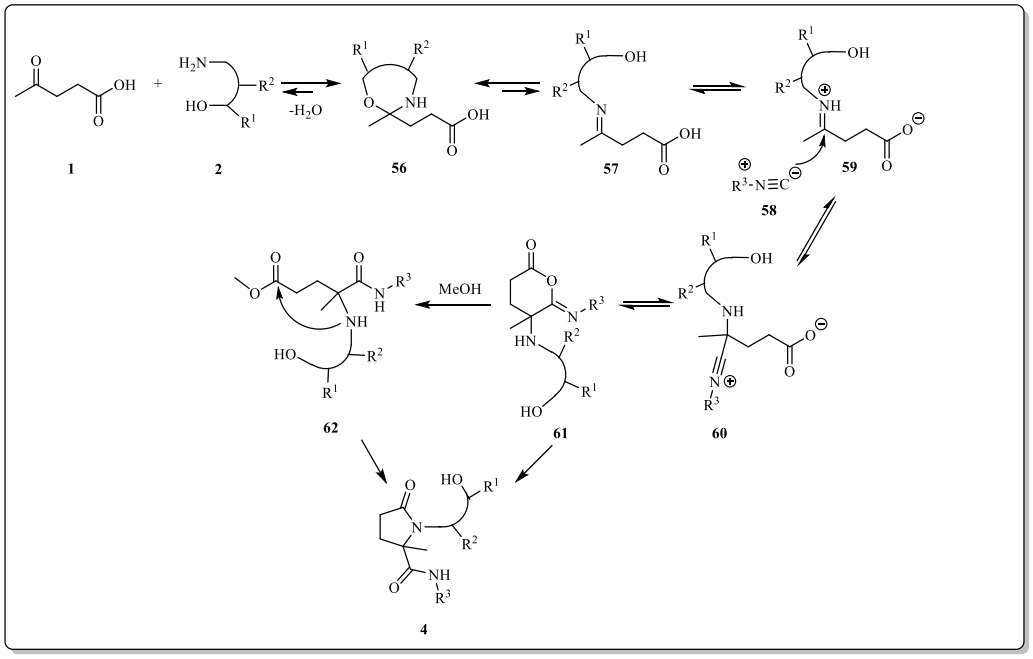
Scheme 9. Multicomponent synthesis of bicyclic heterocycles from levulinic acid.

The planned two-step procedure was first optimized using ethanolamine **2a** and isocyanide **52** (Scheme 10). Using a 1.2:1.2:1.0 stoichiometry of levulinic acid, amino alcohol and isocyanide, an excellent yield of the Ugi reaction was achieved. After a quick liquid–liquid extraction to remove the acid and the amine in excess, product **53a** was obtained in nearly quantitative yield without the need to perform any further purification. Isocyanide **52** was chosen because it is solid, highly stable, and odorless.[42]



Scheme 10. Optimized synthesis of tetrahydropyrrolopirazinedione **55a**.

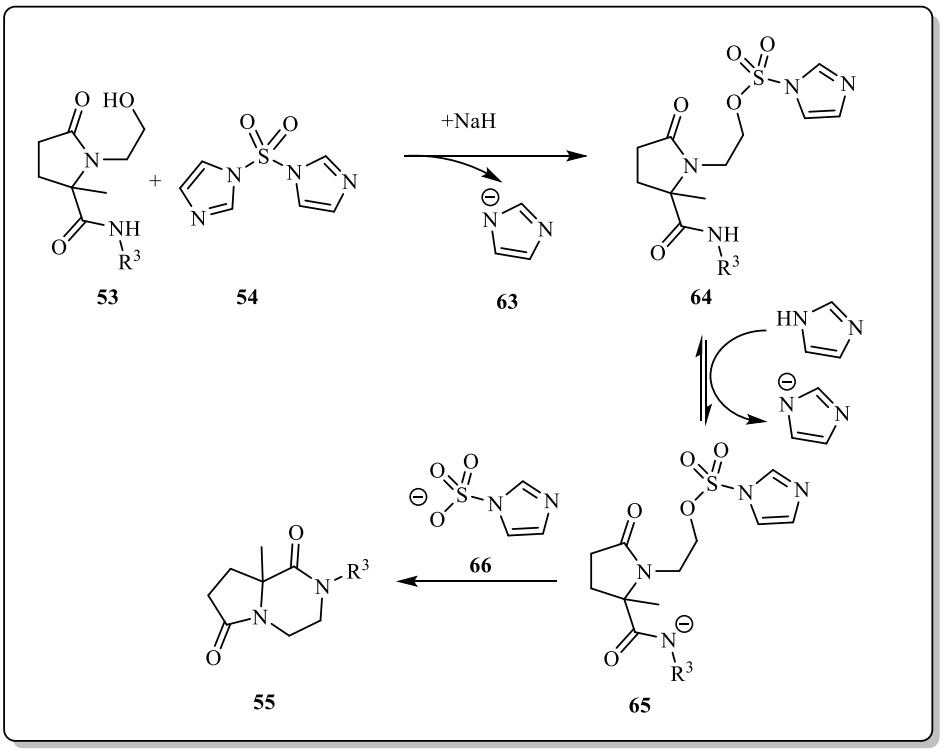
Methanol has been found to be the best solvent according to the mechanism hypothesized by Harriman[43] and shown in Scheme 11. Such mechanism is quite similar to the classical process already described for Ugi reaction. However, after the formation of the cyclic intermediate **61**, Mumm rearrangement is forbidden because of the unfavored formation of a bridging transition state. MeOH provides the ring opening to produce **62**, where an intramolecular nucleophilic attack from the amine group generates the final product. When using a bulkier nucleophile like ^{t}BuOH no reaction occurs. This should confirm the proposed mechanism, although we cannot completely rule out direct rearrangement of **61** into **4**, although difficult for steric reasons.



Scheme 11. Presumed mechanism of the Ugi reaction with levulinic acid and 1,2-amino alcohols.

Mitsunobu reaction did not seem to be the best procedure to use for the cyclization reaction because of its poor atom economy. A two-step procedure involving conversion of the alcohol into a sulfonate was even less attractive from the point of view of operational simplicity. Thus, we chose to employ the combination of sulfonyl diimidazole (SDI) with NaH. This is a methodology firstly introduced by Hanessian.[44,45] Although it is, surprisingly, seldom employed, it was already demonstrated by my group[31] to be an useful alternative to the classical Mitsunobu conditions. SDI is a relatively nontoxic and stable solid. The two reagents are simply added to the solution of the substrate at room temperature without special precautions.

The putative mechanism of the cyclization reaction is shown in Scheme 12. The alkoxide formed by deprotonation with NaH reacts with SDI to form a sulfonate **64**. The deprotonation of the amide by the imidazoline anion **63** promotes an S_N2 displacement of the sulfonate with the consecutive formation of the final product. On aqueous work-up, the leaving group **66** is hydrolyzed to sulfate anion and imidazole. Both these side products are nontoxic and easily removable by liquid–liquid extraction. Imidazole can be recycled and converted back into SDI by reaction with sulfuryl chloride.



Scheme 12. Presumed mechanism of the cyclization with SDI.

Initially the cyclization of **53a** to **55a** was performed in DMF as the solvent. This solvent is typically removed by an extraction using aqueous solution of LiCl, but the polarity of the product and its relative solubility in water makes this procedure unsuitable. The desired specie was indeed partially lost in the aqueous phase during the work-up, lowering the yield.

On the other side, extraction from saturated NH_4Cl was quantitative, but the crude was contaminated by DMF, that was difficult to remove under high vacuum. Moreover, some of the excess of SDI used for the reaction was extracted into the organic phase, contaminating the product **55a**. Although in this particular case a chromatography was able to separate **55a**

from SDI, for other products **55** shown in Figure 2 this was not so easy. Trituration of crude **55a** was tested as an alternative method that could avoid chromatography, but it failed to removed SDI impurity.

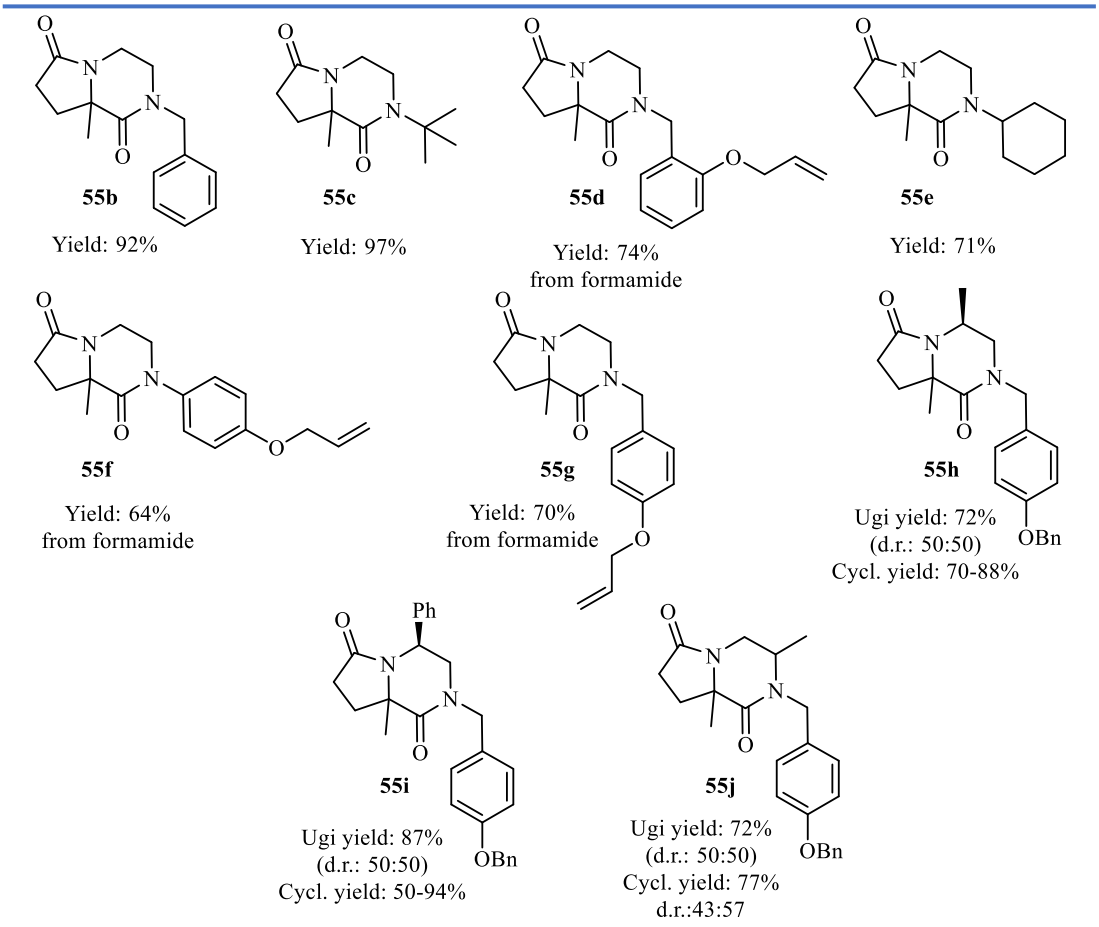


Figure 2. Tetrahydropyrrolopirazinediones prepared. For **55b**, **55c**, **55e**: overall yields of two steps from the isocyanide are reported. For **55d**, **55f** and **55g**: overall yields of three steps from the formamide (precursor of the isocyanide) are reported. For **55h**–**55j**: Ugi product yields are from the chiral amino alcohol, after chromatography. For **55h** and **55i**: the two diastereomers were separated after the Ugi step. Cyclization yields are for the upper and lower diastereomer. (by TLC). In the case of **55j**, the diastereomer. were separated only after cyclization.

When using THF instead of DMF, it turned out to be equally effective to get the product and, more important, it didn't present any problems for the solvent remotion. A different and easy procedure brought the quantitative destruction of the excess of SDI. It consists in adding 0.5 equivalents of inexpensive tris(hydroxymethyl)aminomethane (TRIS) which, in the presence of excess NaH, reacts with SDI to form a water soluble cyclic sulfate. In this way, an extractive work-up became sufficient to obtain a pure product, making chromatography unnecessary. The presented procedure is advantageous from different point of view. The overall yield is indeed quite high and, moreover, both steps are performed at room temperature, without particular precautions to avoid humidity. Finally, all side products can be removed through a simple liquid-liquid extraction after the two single steps. The results obtained for other pyrrolopirazinediones with good to excellent yield (Figure 2) confirm the efficiency of this methodology. Compound **55b** was previously reported by Hulme *et al.*[28]

using the approach depicted in Scheme 8 (R^1 = H, R^2 = Bn). In that case the benzyl group (R^2) did not derive from the isocyanide, but from a Boc-protected amino alcohol instead, and the overall yields were lower. The overall yield shown for compound **55f** has not to be confused with an unsatisfactory result because it was calculated on three steps, starting from the corresponding formamide. The latter was used to prepare the isocyanide *in situ* using the Burgess reagent.[46] This procedure was chosen because of the known poor stability of aromatic isocyanide and, thus, in order to have a more operationally simple method. Actually, the cyclization itself was again very efficient, proceeding in 95 % yield. In the case of compounds **55d** and **55g**, the required benzyl isocyanides were obtained from the corresponding formamides ad purified by chromatography. However, due to their partial volatility, we did not dry them exhaustively, and thus also in this case the yield was calculated from the formamide. Although this bicyclic system is still poorly explored in medicinal chemistry, a recent patent has shown activity of tetrahydro-pyrrolopiperazines as neurokinin 1 receptor antagonists.[40] Moreover, some natural alkaloids (*e.g.* paraherquamides and aspergillimides), that contains this scaffold, have antihelmintic or neuroprotective activity.[47]

Then, in order to further expand diversity, we explored the use of chiral 1,2-amino alcohols derived from α-amino acids. The ratio between reagents was varied using a slight excess of isocyanide because of the preciousness of the amino alcohol. The Ugi reaction suffered the change of the amino alcohol. The formation of a concurrent Passerini product was indeed observed. Trifluoroethanol typically favors the formation of Ugi product when it is used as solvent because its polarity produces a stabilization of the nitrilium ion which is formed during the reaction. In this particular case, however, its use brought the formation of only the Passerini product. This, again, confirms the role of MeOH in opening the intermediate **61** (Scheme 11). The formation of the concurrent product was completely suppressed by simply preforming the intermediate oxazolidine **56** (Scheme 11). Thus, equimolar quantities of the chiral amino alcohol and levulinic acid were mixed in methanol for 2 h in the presence of molecular sieves, before addition of the isocyanide. Using this modification, the Ugi product yields were again good. On the other hand, the diastereoselectivity, as it often happens in isocyanide-based MCRs, was very poor. However, the two Ugi diastereomers could be separated and submitted independently to the next step.

Cyclization was slower and only low or moderate yields were obtained in THF. By shifting to DMF and, in some cases, by increasing the temperature, all reactions were brought to completion. Interestingly, the rate of cyclization was remarkably lower for one of the two diastereomers. This is reflected in the different cyclization yields for the two diastereomers of **55h** and **55i**. In both cases the less polar diastereoisomer behaved poorly in this step.

1-amino-2-propanol was also employed, in racemic form. In this case the two Ugi diastereomers could not be separated at this stage, but only after cyclization. The different yields measured shows that also in this case cyclization is favored for one of the two diastereomers.

This protocol was then extended to the obtainment of the hexahydro pyrrolodiazepinediones **67** depicted in Figure 3. The Ugi reactions using propanolamine as component proceeded without particular problems, but also in this case premixing the amino alcohol and levulinic acid better yields were obtained. On the other side, the first test to produce **67a** using THF as solvent produced only poor yield. Replacing the latter with DMF

the reaction worked better, even if the yield was lower than those obtained for six-membered adducts. In this case very polar side-products containing the imidazole ring were detected. It may indicate that the intermediate sulfonate **64** (see the mechanism depicted in Scheme 12) may also be displaced by the imidazolide anion **63**.

When starting from cyclohexyl isocyanide the use of SDI under the usual conditions with DMF produced only poor yield (27 % at room temperature and 28 % at 50 °C) and the polar side products became predominant, probably because of the higher steric bias of the nucleophilic nitrogen. Then, an alternative strategy was proposed. It consists in the formation of a methanesulfonate that can be submitted to cyclization using NaH in DMF (method B, Figure 3). A higher yield of 60% was achieved using this strategy. My own contribute was inserted at this level in order to expand the reaction scope.

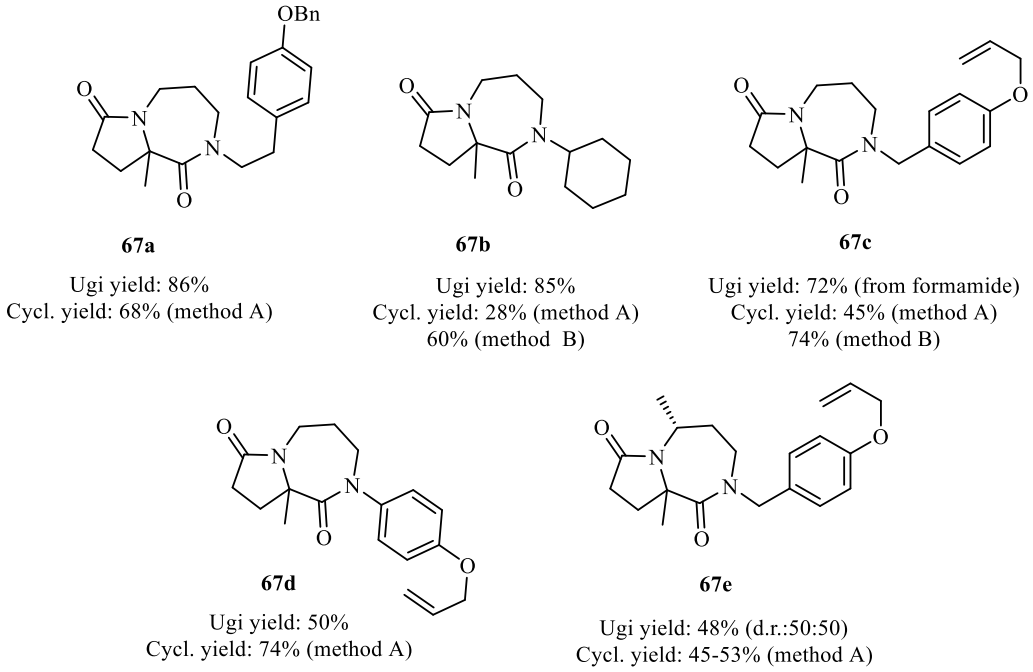


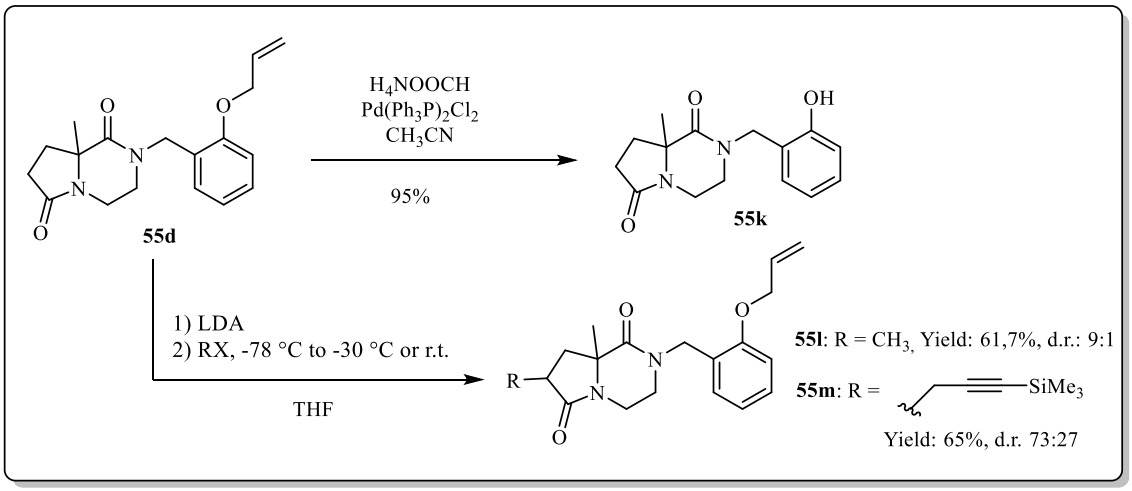
Figure 3. Hexahydropyrrolodiazepinediones prepared. Method A: SDI, NaH, DMF, 50 °C. Method B: 1) MsCl, Et_3N, CH_2Cl_2; 2) NaH, DMF, 50 °C. For **67c** and **67d** the Ugi yield is calculated from the formamide (precursor of the isocyanide). For **67e** the Ugi yield is calculated from the amino alcohol. In the case of **67e** the two diastereomers were separated after the Ugi step and cyclized independently. Cyclization yields are for the upper and lower diastereomer (by TLC).

The synthesis of pyrrolodiazepinedione **67c** had already been noted to be sensitive to the use of method A with the production of side-products formed by the nucleophilic attack of imidazole anion towards the sulfonate intermediate. Thus, method B was favored for this synthesis obtaining a yield of 74%. The only problem of this procedure is that during the aqueous work-up at pH = 5 among the two steps, a little percentage of the methanesulfonate intermediate is hydrolyzed and the Ugi product is again produced. From this point it won't be no more converted in the final product. With the combination of SDI and NaH, instead, we need just to add other equivalents of these two species to go on with the reaction. When the nitrogen of the secondary amide is linked directly to the aromatic ring the sulfonate

intermediate will be less sensitive to the attack of the imidazole anion and the method with SDI and NaH becomes again efficient for the obtainment of product **67d**. The two diastereomers which were obtained as Ugi adducts starting from a chiral enantiopure propanolamine showed a different reactivity in the cyclization reaction, but method A produced good results for the synthesis of both diastereomer of **67e**.

As it can be seen in Figure 2 and Figure 3, several of the adducts prepared contain a protected phenol. This follows recent interest of my research group in the synthesis of artificial phenols from natural phenolic building blocks.[48] The allyl group was selected by us as an ideal protecting group for the phenolic moiety, since it can be deblocked under neutral conditions. As an example, previous work showed the high deprotection of compound **55d** to give the free phenol **55k**, Scheme 13.

The pyrrolidinone ring had already been noted to be able to be further functionalized through enolate chemistry. Scheme 13 shows the α-alkylation of the lactam with two different electrophiles. These alkylations were found to be diastereoselective, especially in the case of methylation.



Scheme 13. Further reactions performed on pyrrolopiperazinedione **55d**. Yields for **55k** and **55l** are calculated from unrecovered **55d**.

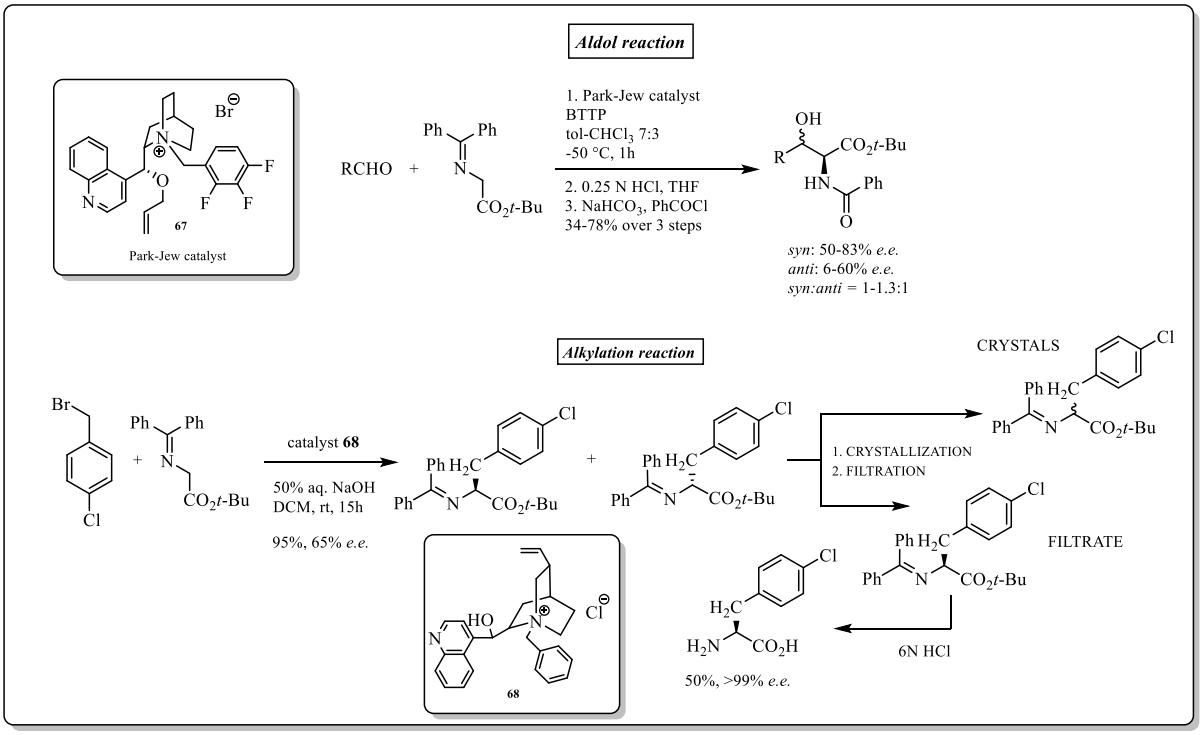
In conclusion, an operationally simple and high yielding methodology to convert levulinic acid into tetrahydro pyrrolopiperazinediones was developed. The procedure is endowed with operational simplicity consisting in simply mixing the reagents at room temperature. Albeit the higher strain of the seven membered ring makes the cyclization less efficient, it is worth noting that this represents the first example of synthesis of seven-membered rings through S_N2 cyclization of an Ugi-derived secondary amide onto an alcohol (or halogen) leaving group.[49] This bicyclic scaffold is nearly unexplored, but, due to its drug-likeness, it is expected to be promising in medicinal chemistry as well.[50]

2.3 Synthesis of new potential organo-catalysts

2.3.1. Chiral amines in organo-catalysis

As introduced in chapter 1, the main part of my work regarded the synthesis of new potential organo-catalysts employing multicomponent reactions in the synthetic pathway. All strategies were aimed towards the obtainment of tertiary and secondary amines.

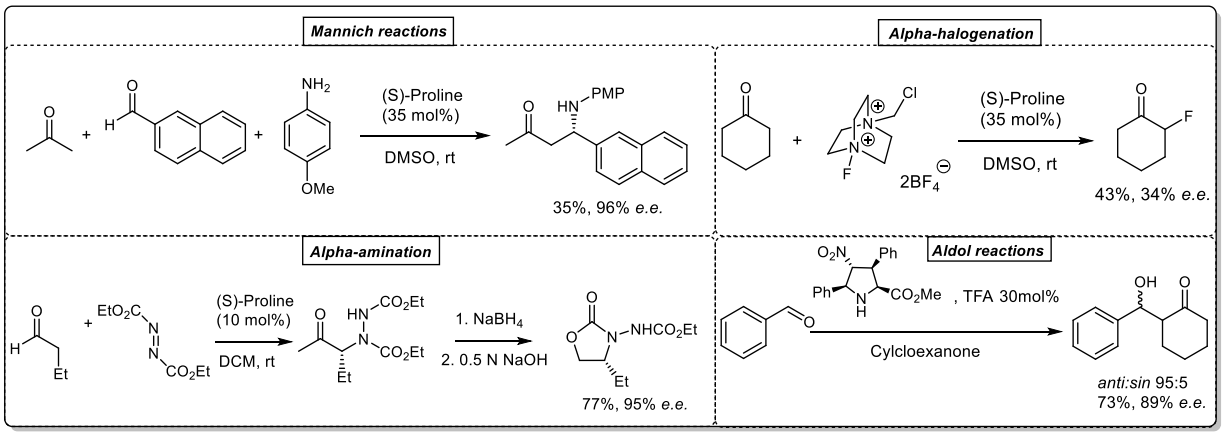
The examples of processes which are catalyzed by secondary or tertiary amines are many in the literature. The first ones are involved in catalysis *via* enamine or iminium ion, whereas the second ones are employed as quaternary ammonium salts in phase transfer catalysis or as such in base-catalyzed processes. Corey and O'Donnell reported the viability of *Cinchona* alkaloids for the synthesis of β-hydroxy α-amino acids *via* aldol reactions,[7] a topic first explored by Miller and Gasparski, and *via* alkylation of the benzophenone Schiff base of *tert*-butyl glycinate (Scheme 14).[8]



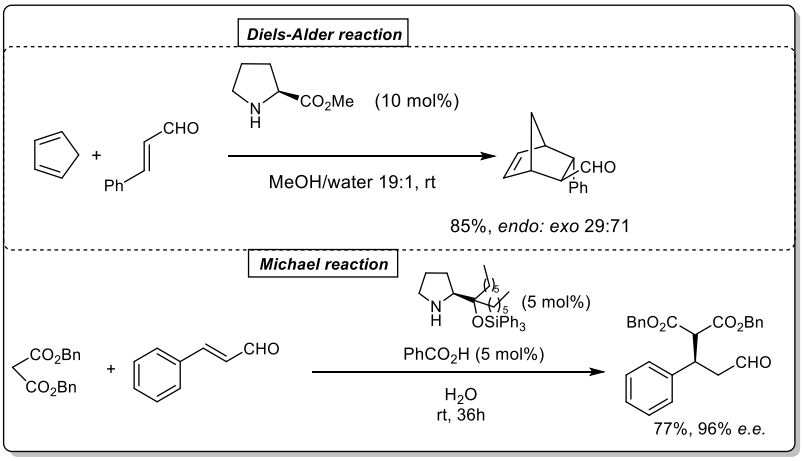
Scheme 14. Reactions catalyzed by *Cinchona* alkaloids

The mechanistic reasons of the high enantioselectivity of these reactions are kept inside a specific three-dimensional arrangement of a contact ion pair in which a nucleophilic site of the substrate is proximate to the quaternary cationic center among which there is an optimum van der Waals attractive interaction.[51] Direct asymmetric Mannich reactions of ketones,[52] α-amination,[53] aldol reactions[54] and α-halogenation[55] (Scheme 15) are only few examples of reactions that can be catalyzed by chiral secondary amines through enamine catalysis. It is based on the reversible generation of enamines from a catalytic amount of an amine and a carbonyl compound. The highest occupied molecular orbital (HOMO) of the enamine is higher in energy than the HOMO of the carbonyl compound. Thus, it can more easily interact with the lowest unoccupied molecular orbital (LUMO) or singly occupied molecular orbital (SOMO) of an electrophile.[9]

The iminium ion catalysis is used for example in Michael[56] and Diels-Alder[10] reactions (Scheme 16) to activate α,β-unsaturated carbonyl compounds through their reversible condensation with chiral amines to form an iminium ion. Its LUMO is lower in energy and this results in an enhanced electrophilicity and therefore can more readily interact with nucleophiles.[9]

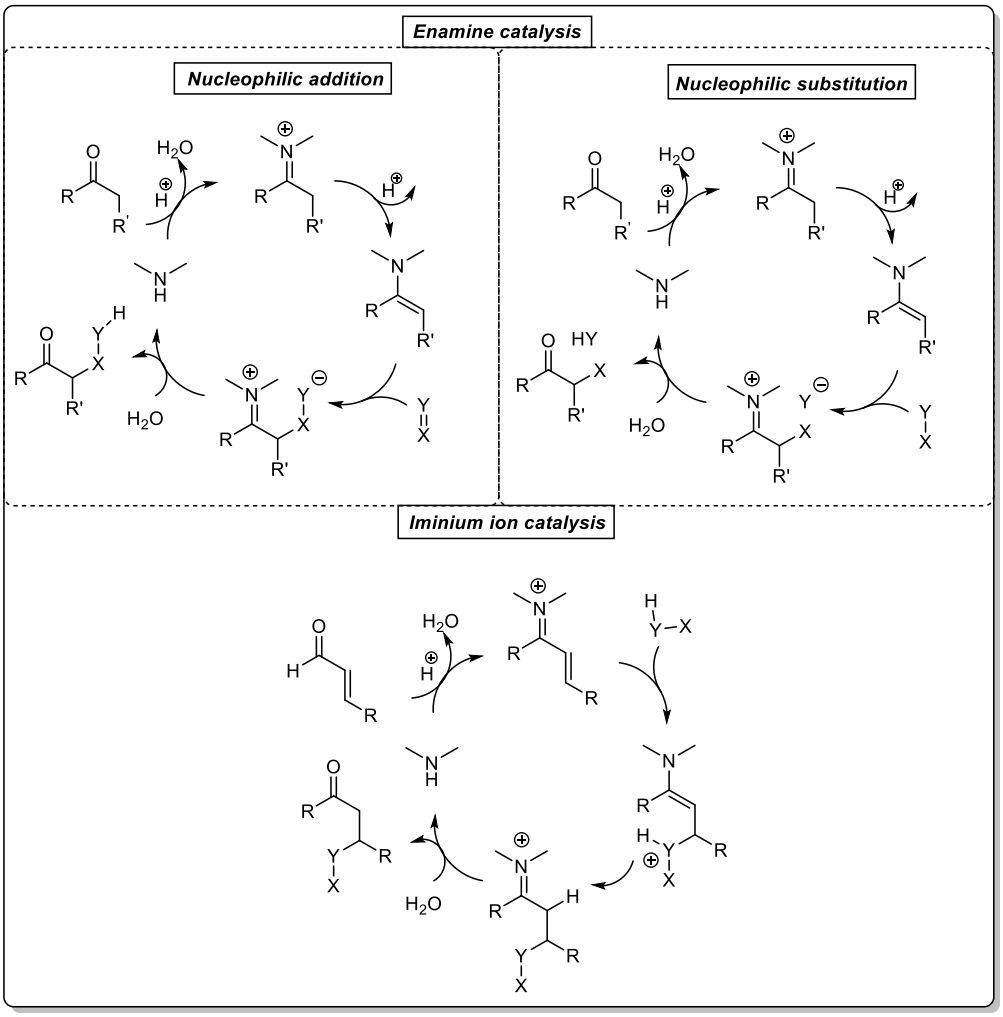


Scheme 15. Enamine-catalysis examples.

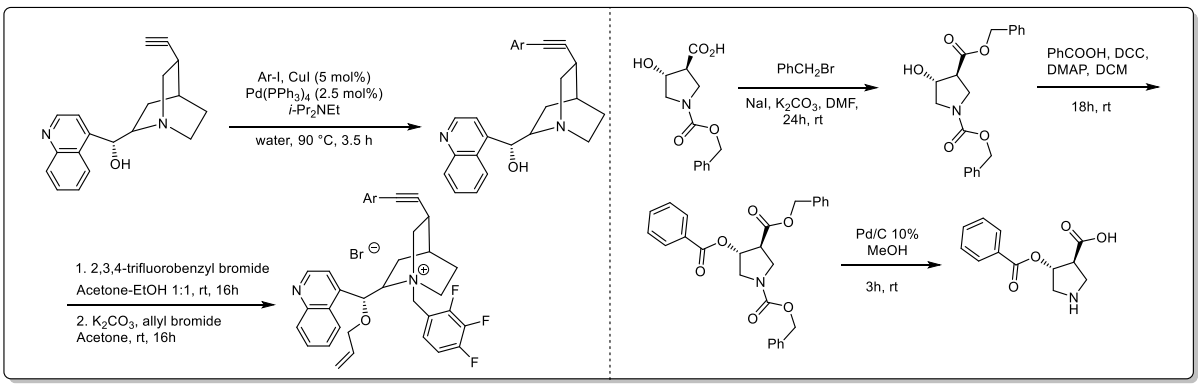


Scheme 16. Iminium ion-catalysis examples.

The catalytic cycles of this kind of catalysis are reported in Scheme 17. The modification of these catalysts often requires target-oriented synthetic pathways (Scheme 18).[7,51] In spite of these structural modifications, they remain *Cinchona* and proline derivative. Thus, an alternative strategy to obtain new catalysts with new scaffolds would be desirable.



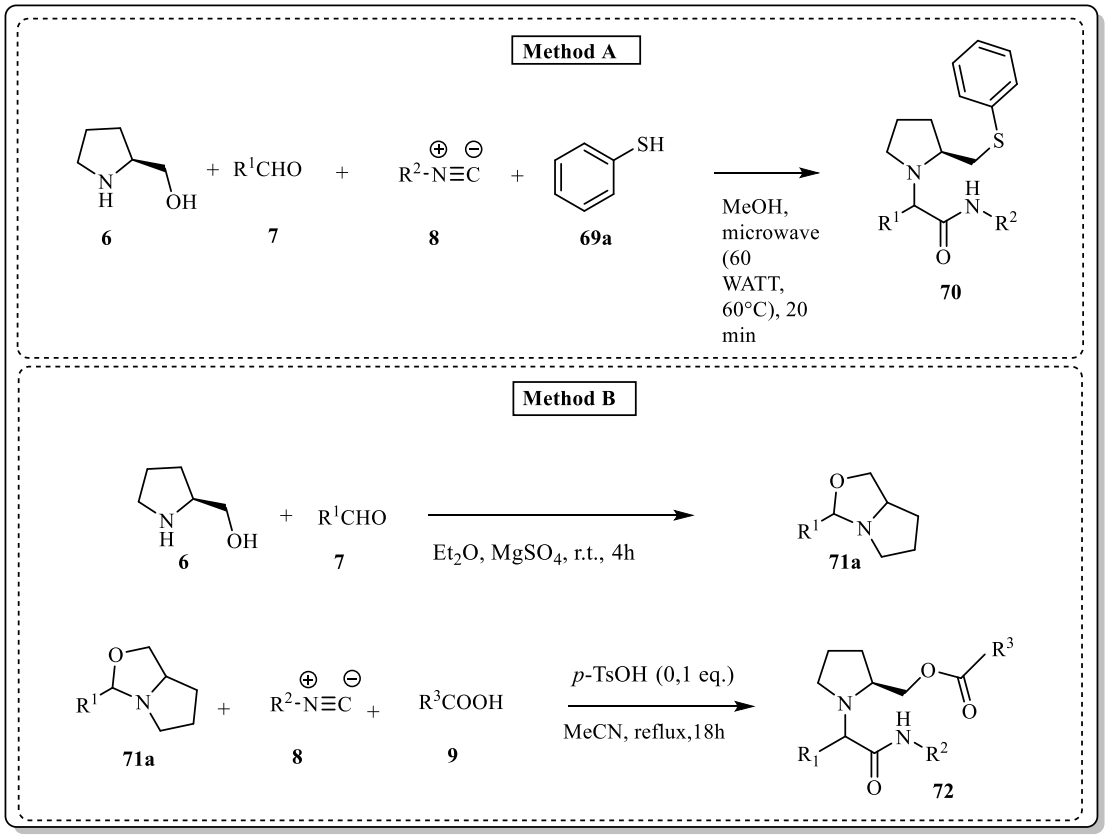
Scheme 17. Catalytic cycles with secondary amines as catalysts.



Scheme 18. Synthesis of catalysts.

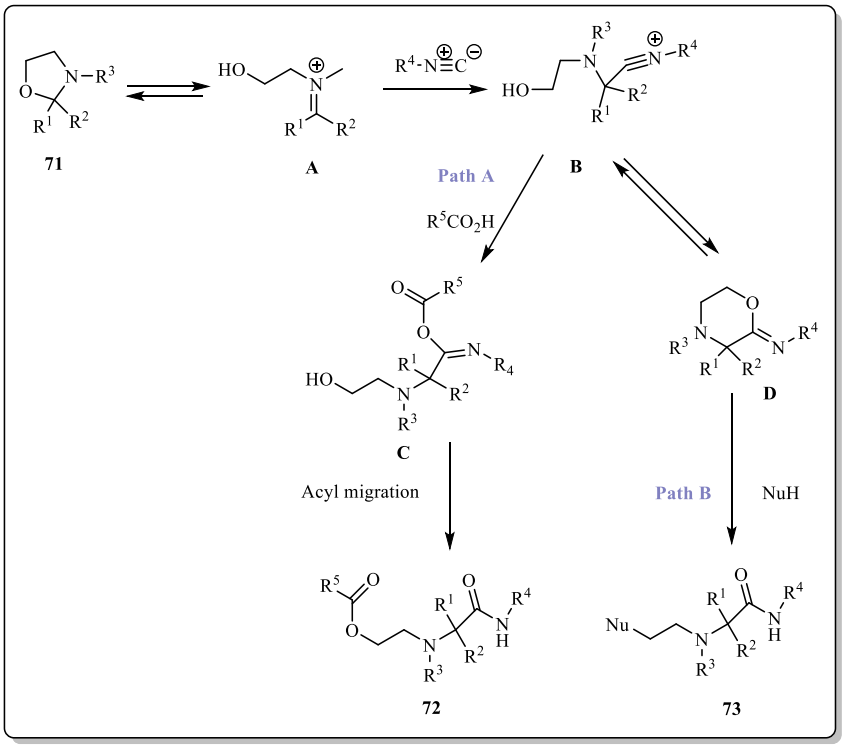
2.3.2 Multicomponent synthesis of chiral tertiary amines from prolinol

Sheppard and coworkers reported that replacing the amine with an amino alcohol it is possible to shift from classical Ugi products towards new scaffolds having tertiary amine groups. They employed chiral secondary amino alcohols, including L-prolinol **6**, and reported two different methods leading to tertiary amines. The first one involves prolinol **6**, an aldehyde, an isocyanide and thiophenol (Scheme 19, method A).[12] In the second strategy thiophenol is replaced with a carboxylic acid (Scheme19, method B).[13]



Scheme 19. Multicomponent reactions involving L-Prolinol **6**.

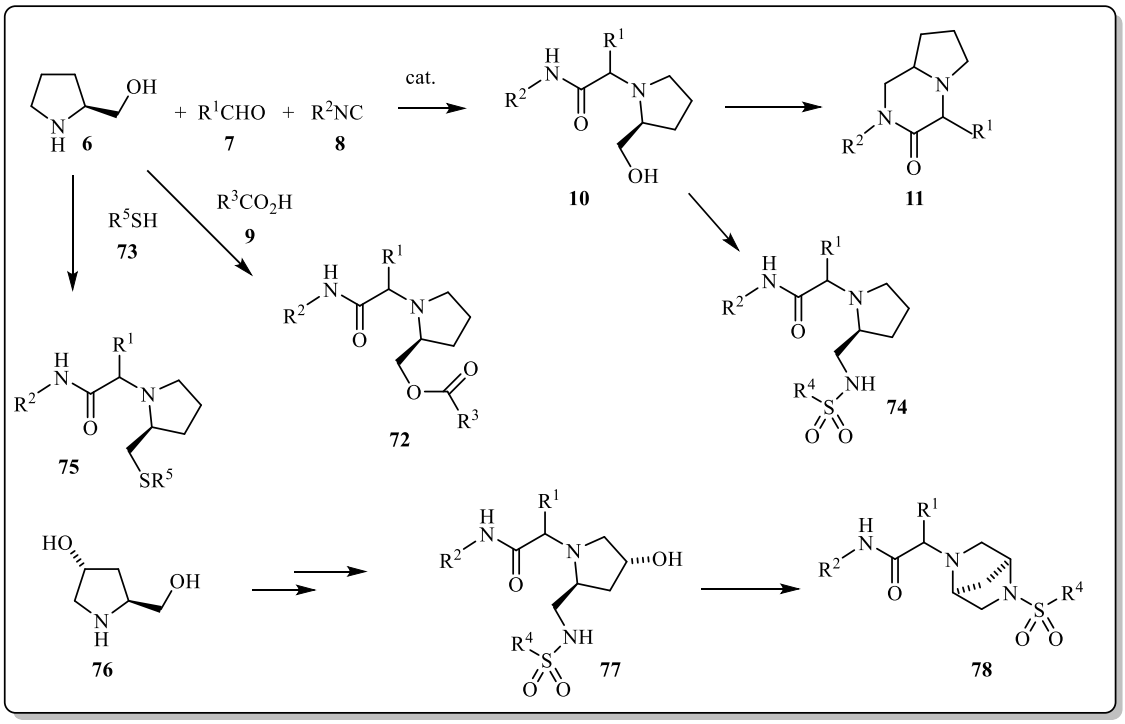
These reactions proceed with excellent diastereoselectivity. A single diastereoisomer is indeed formed and this is unusual for Ugi and Ugi-type reactions. Based on the type of acid the reaction mechanism can follow two paths. One follows the classical steps of Ugi reaction (path A, Scheme 20), but the acyl group migrates on the hydroxyl function instead of the amine function. This is because the intermediate **B** contains a tertiary amine where the acyl group is not able to migrate. When the carboxylic acid is replaced with thiophenol the softer nucleophilic character of this specie allows the nitrilium ion to rearrange and produce the cyclic intermediate **D** which is then involved in the production of the final product **73** (path B, Scheme 20).



Scheme 20. Proposed mechanism with amino alcohols.

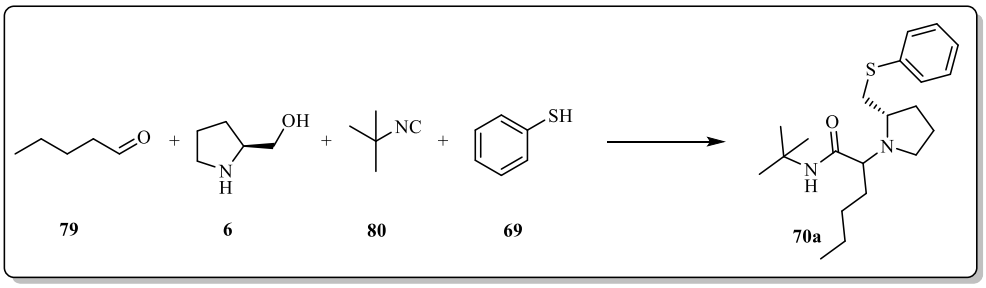
On these bases my work was initially aimed to the synthesis of tertiary amines starting from L-Prolinol **6**. A thiol and a carboxylic acid were chosen as nucleophile species in order to employ the methodologies reported by Sheppard to expand the reaction scope with the use of other aldehydes and isocyanides, also studying the change in the diasteroselectivity.

Looking again at the mechanism, if no nucleophile is present, or if it reacts only slowly, the reaction should stop at the level of cyclic intermediate **D** (Scheme 20). Then, during work-up, it would be hydrolized to give the truncated product **10** (Scheme 21). It can be interesting because the alcoholic group could be employed for further functionalization. Mitsunobu or Mitsunobu-like reactions are suitable for the scope. First, an intermolecular interaction with a sulfonamide could be tested as first approach to the study on the potentiality of the truncated product **10**. Intramolecular cyclization could be then explored to obtain bicyclic and, thus, more rigid structures like **11**. Following this approach, other prolinol derived compounds like **78** should give the chance to go on in the exploration of chemical diversity to obtain even more complex structures.



Scheme 21. Synthetic project for the synthesis of tertiary amines.

Initially, my work was dedicated to the multicomponent synthesis of compound **70a** (Scheme 22). ^{t}Butyl isocyanide was chosen being commercially available and giving the chance to avoid the synthesis of other potentially unstable isocyanides. Pentanal **79**, as aliphatic aldehyde, allowed us to adhere more closely to the methodologies described above (actually, Sheppard *et al*. used aliphatic aldehydes like heptanal and butanal instead of pentanal).



Scheme 22. Synthesis of compound **70a** starting from L-Prolinol.

Surprisingly, perfectly reproducing the reported reaction conditions, no reaction occurred (entry 1, Table 1). Thus, different reaction conditions were tested. All tests were performed with molecular sieves to favor the formation of oxazolidine. In most cases it was preformed by simply mixing the aldehyde and prolinol in the solvent. MeOH resulted to be the best solvent producing better results than trifluoroethanol (entry 2 and 4, Table 1), which should stabilize the nitrilium intermediate thanks to its higher polarity. An increasing of temperature up to 100 °C was required to obtain the best results (entry 5, Table 1), probably indicating the thermodynamic push required to allow the opening of the intermediate **D** (Scheme 20). This intermediate also requires a sufficient amount of thiophenate to be opened. Thus, Et_3N was used to guarantee the formation of sufficient amount of thiophenate but it

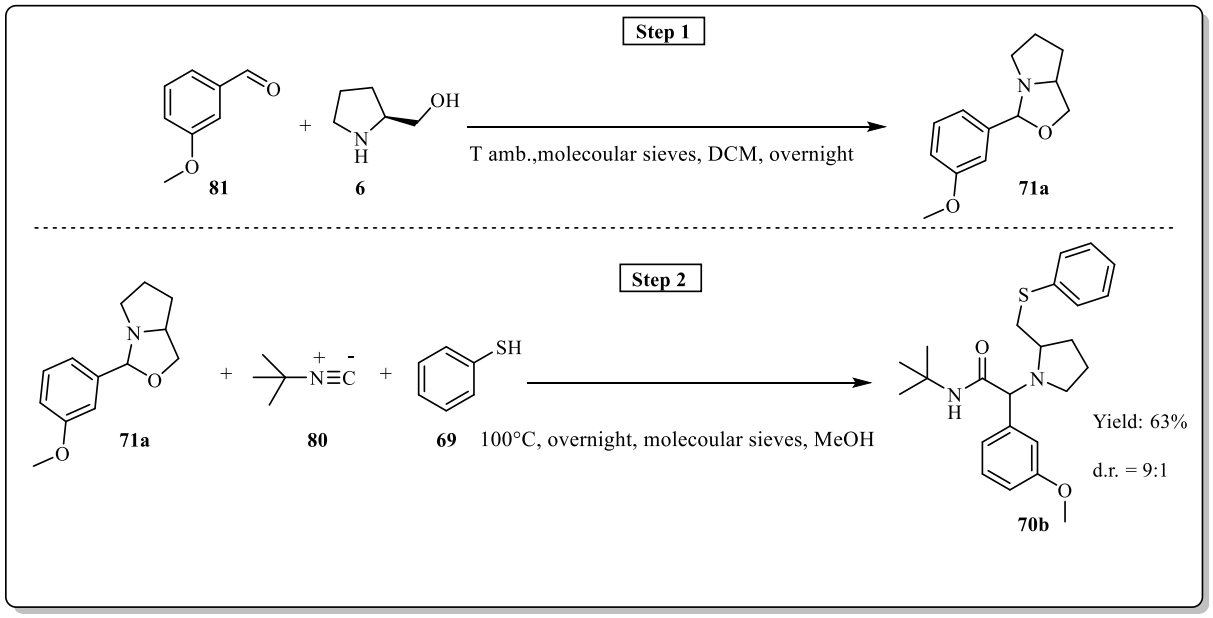
brought the reaction to be less clean and various not easily recognizable side product were detected (entry 6, Table 1).

Table 1. Optimization for the synthesis of **70a**.

Entry	Solvent	Additives	Molecular sieves	t	T (°C)	Yield (%)
1	MeOH	/	/	20 min	Microwave (60 W, 60 °C)	/
2[a]	MeOH	/	100 mg	4 h	r.t.	33
3[a]	MeOH	/	100 mg	overnight	reflux	32
4[a]	CF_3CH_2OH	/	100 mg	overnight	reflux	2
5[a]	MeOH	/	100 mg	overnight	100	50
6[b]	MeOH	Et_3N	100 mg	overnight	100	8
7[a]	MeOH	/	100 mg	overnight	120	16

The reaction progress was followed through TLC. [a]First only **79** and **6** were added in the solvent and the reaction was stirred for 2h at r.t. to favor the formation of oxazolidine. Then **78** and **69** were added. [b]First only **79** and **6** were added in the solvent and the reaction was stirred for 2h at r.t. to favor the formation of oxazolidine. Then **80**, **69** and Et_3N (0.170 µL, 1.22 mmol) were added.

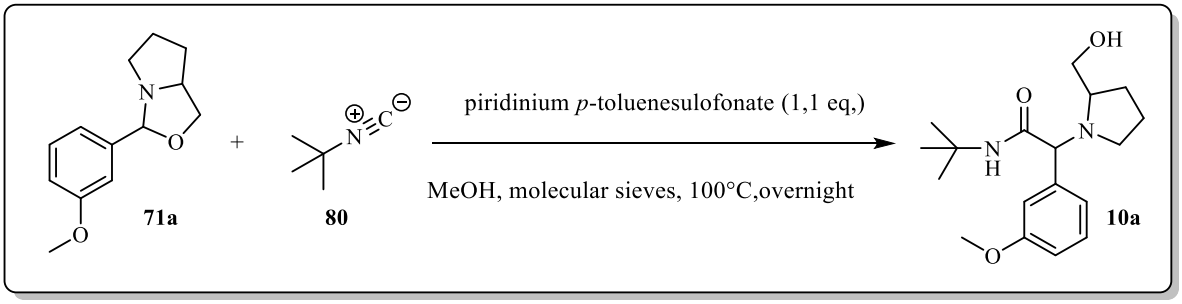
Again, based on the conditions reported by Sheppard (method B, Scheme 19), I tried to preform the oxazolidine using Et_2O as solvent and $MgSO_4$ to eliminate water and move the equilibrium of the reaction towards the product. At this stage we decided to shift to an aromatic aldehyde, which offers the chance to better follow the reaction though TLC. Thus, I chose to use a *meta* substituted methoxybenzaldehyde, because previous work in my lab has shown that *para* or *ortho* substituted alkoxybenzaldehyde tend to be less reactive in Ugi reactions (Scheme 23). The problem was that, in the first step, I got less product than the expected quantity, although the formation of the oxazolidine was almost complete. The reason could be that being $MgSO_4$ a Lewis acid it could hold back the product during the filtration of the mixture reaction, so we couldn't get the product with good yields. With DCM, instead, the reaction was complete and I got the expected quantity of oxazolidine.



Scheme 23. Synthesis of *N*-(*tert*-butyl)-2-(3-methoxyphenyl)-2-(2-((phenylthio)methyl)pyrrolidin-1-yl)acetamide **70b**.

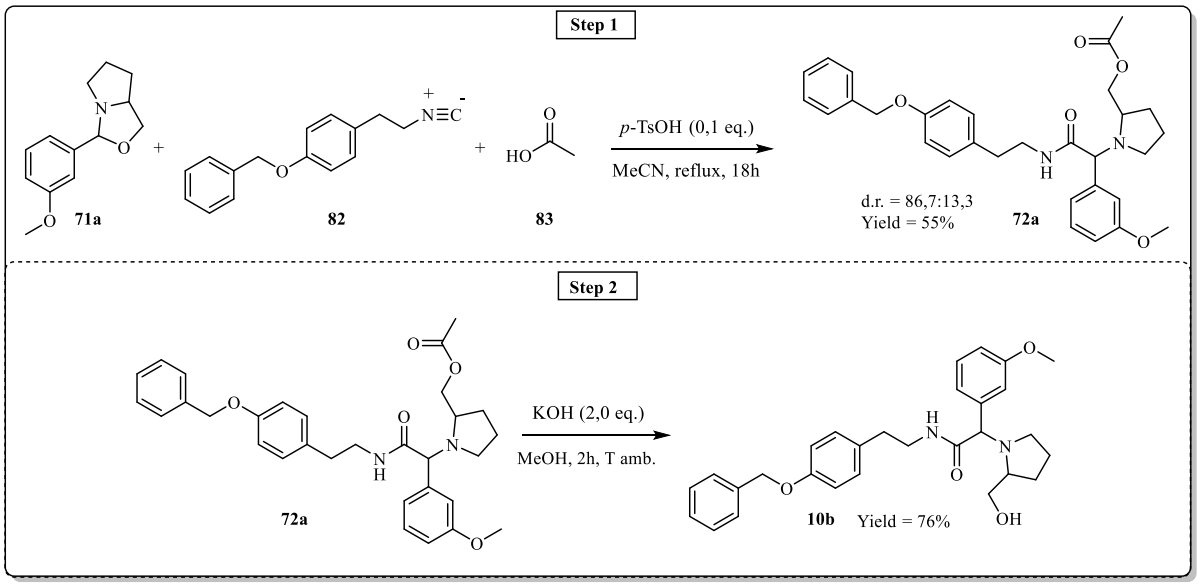
Thus, from the point of view of the yield, we were satisfied by these optimized conditions. The nature of the aldehyde slightly influences the diasteroselectivity of the reaction. While I noted the formation of one diastereomer with the aliphatic aldehyde **79**, we got a d.r. = 9:1 with compound **72**.

As introduced at the beginning of this chapter, truncated Ugi specie **10** shows a free alcohol group that makes it desirable as product. Thus, I looked for a method to get it efficiently. First, I tried its synthesis performing the multicomponent reaction with the preformed oxazolidine and the isocyanide, using pyridinium *p*-toluenesulfonate to favor the opening of the cyclic intermediate **D** (Scheme 20).



Scheme 24. Proposed synthetic pathway for the obtainment of **10a**.

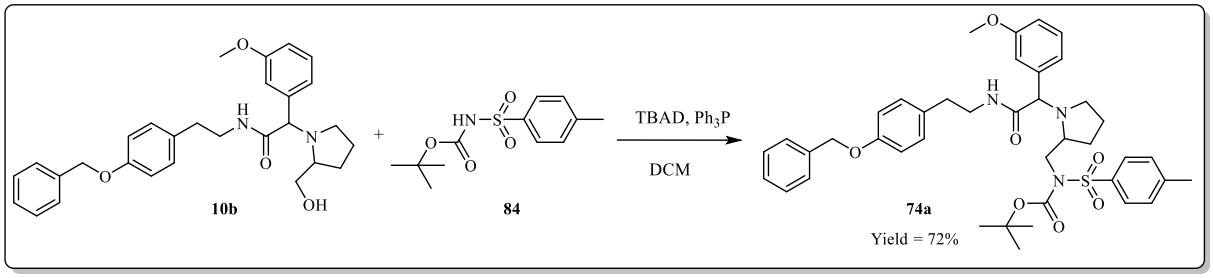
Unfortunately, this test produced only unidentified side-products. A two-step procedure was, then, planned. First, a multicomponent reaction with acetic acid was performed (Scheme 25) to obtain an ester function. Isocyanide **82** was used to follow more easily the formation of side products. Even in this case a complete diastereoselectivity was not detected. Moreover, the two diastereomers were not able to be separated by chromatography. As it can be observed, the product contains an ester function. It offers the chance to obtain the final desired product **10b** with a very simple hydrolysis reaction under basic conditions.



Scheme 25. Synthesis of truncated Ugi-product **10b**.

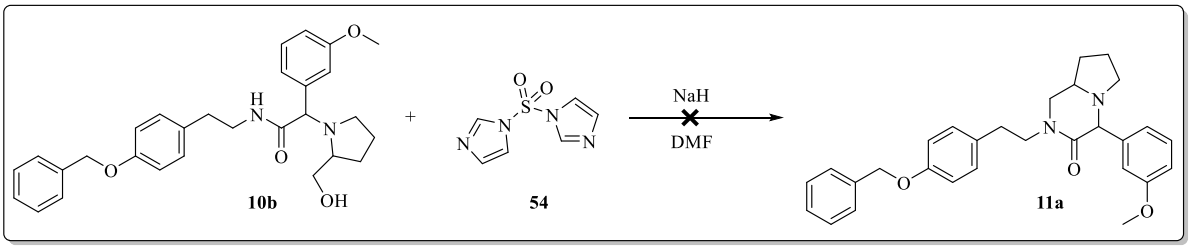
In order to explore the real potentiality of the linear compounds synthesized through multicomponent reaction, we studied the susceptibility of the hydroxylic group to a

functionalization with an intermolecular Mitsunobu reaction (Scheme 26). The reaction indeed worked in good yield and the two diastereomers could be separated.



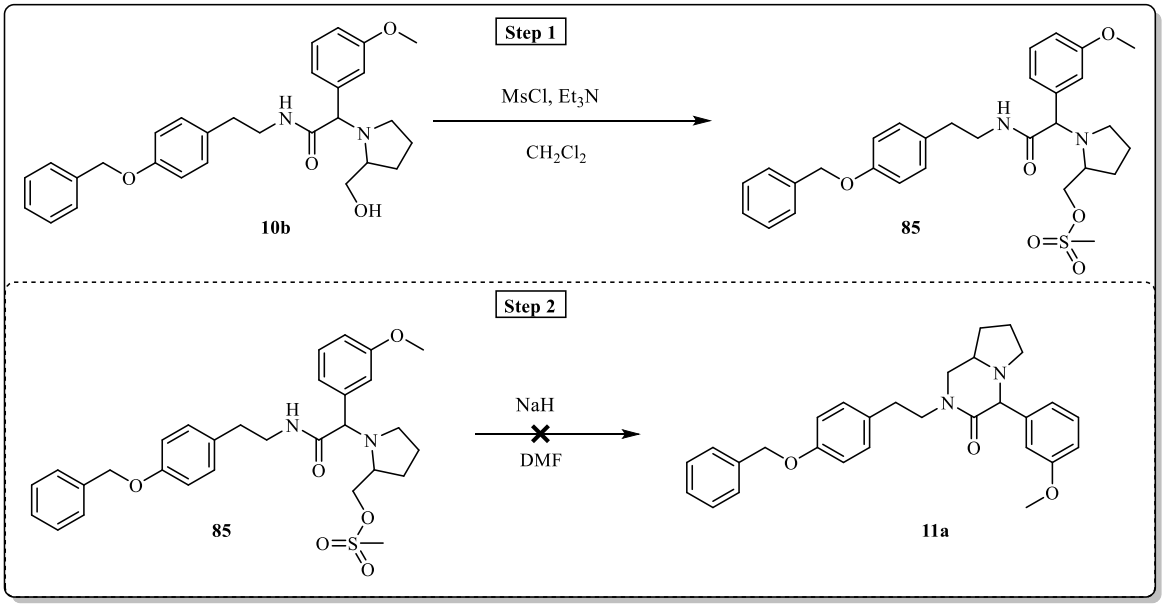
Scheme 26. Mitsunobu reaction.

Thus, we investigated the possible cyclization by a nucleophilic substitution involving the isocyanide derived secondary amide as nucleophile and the primary alcohol as electrophile. This reaction has been often studied in my group, but never on a substrate containing a tertiary amine. SDI and NaH were employed (Scheme 27).



Scheme 27. Proposed strategy for the synthesis of bicyclic products.

Unfortunately, I did not get the hoped results, but just products with an unidentified structure. I tried to exploit a cyclization going through a methansulfonate intermediate **85** (Scheme 28), but without better results.



Scheme 28. Proposed strategy *via* methansulfonate for the synthesis of bicyclic products.

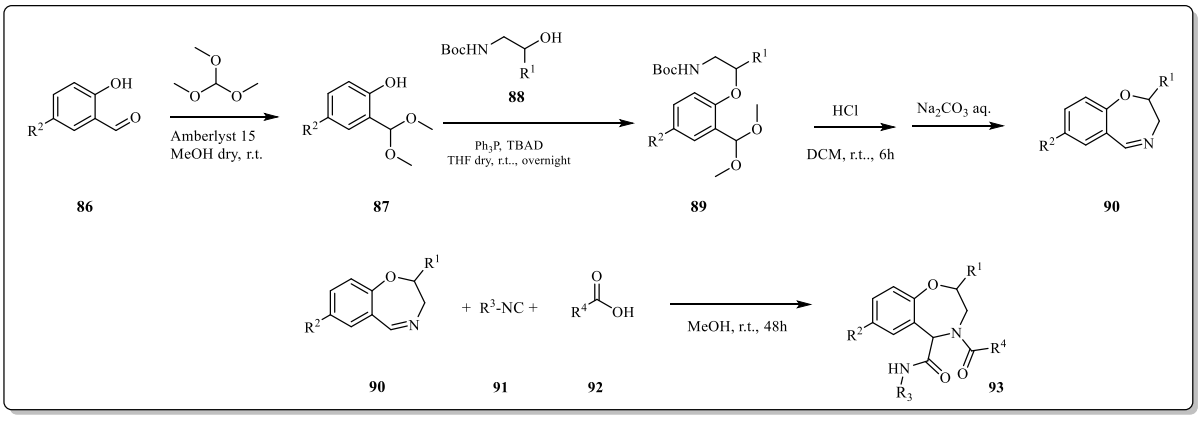
The intermediate **85** resulted very fleeting and its instability brought to the formation of other products, always not so easily identifiable.

Briefly resuming, the synthesis of tertiary amines starting from L-prolinol showed different problematics, starting from their synthesis, where many side products tend to form. However, the synthetic strategy to get them is almost optimized. The truncated product was difficult to be obtained through a direct multicomponent reaction. Anyway, I showed that it can be prepared also through two very simple steps. Moreover, it is sensitive to a further functionalization. The diasteroselectivity of this kind of Ugi reaction is quite high and substrate dependent. When two diastereomers are formed they result separable by chromatography just after intermolecular Mitsunobu reaction, and this hamper their utilization as organocatalysts.

Before studying other strategies to get intramolecular-functionalizations, the work was shifted towards the obtainment of secondary amines. As it has been widely discussed, Ugi-type reactions produces peptide-like products. Thus, I moved towards the research of a method that would employ a multicomponent process with high degree of diastereoselectivity and, more important, allow to convert the amide of the multicomponent adduct into a secondary amine group.

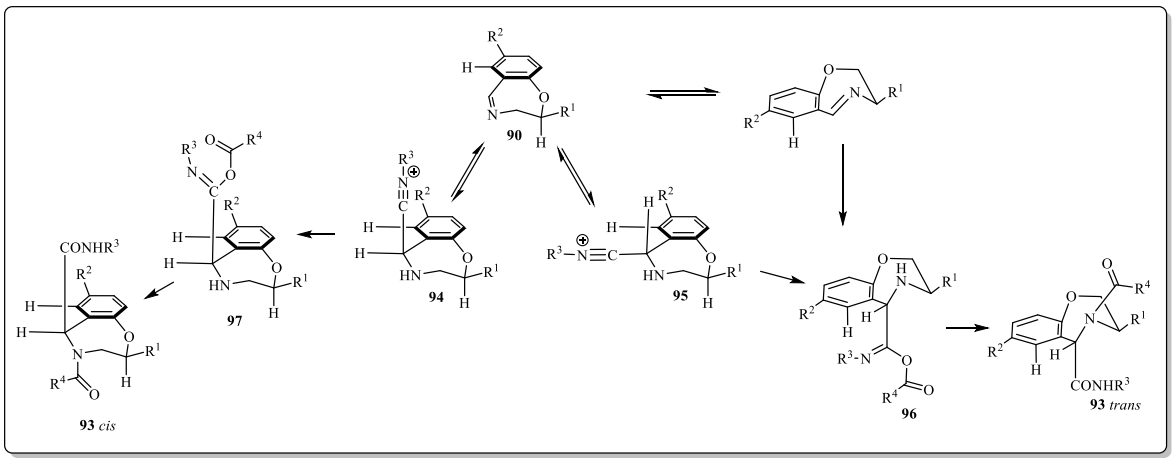
2.3.3. Synthesis of chiral seven-membered amines through diastereoselective Ugi-Joullié reaction

Recently, my research group was involved in the synthesis of tetrahydrobenzoxazepines (Scheme 29).[14] The methodology involves a starting Mitsunobu reaction between the protected form of salicyl aldehyde **87** and a Boc-amino alcohol **88**. The treatment of the product with acid conditions produces in sequence the deprotection of the aldehyde and the amine group and a final basic work-up brings the spontaneous cyclization reaction to form **90**. This cyclic imine is then involved in an Ugi-Jollié type reaction. Ugi-Joullié reaction is one more example of MCR which brings to not classical Ugi-products. It involves a cyclic imine, an isocyanide and a carboxylic acid (Scheme 29).[57] Most examples of this reaction regard five membered rings such as pyrrolines and thiazolines. Good diastereoselectivity have been obtained only in a few cases. Most of them involves five-membered imines with a stereogenic center α to the imine carbon.[58-60] Only moderate diastereoselectivity is achieved with cyclic imines having the stereogenic center α to the nitrogen.[61,62]



Scheme 29. Synthesis of tetrahydrobenzoxazepines **93**.

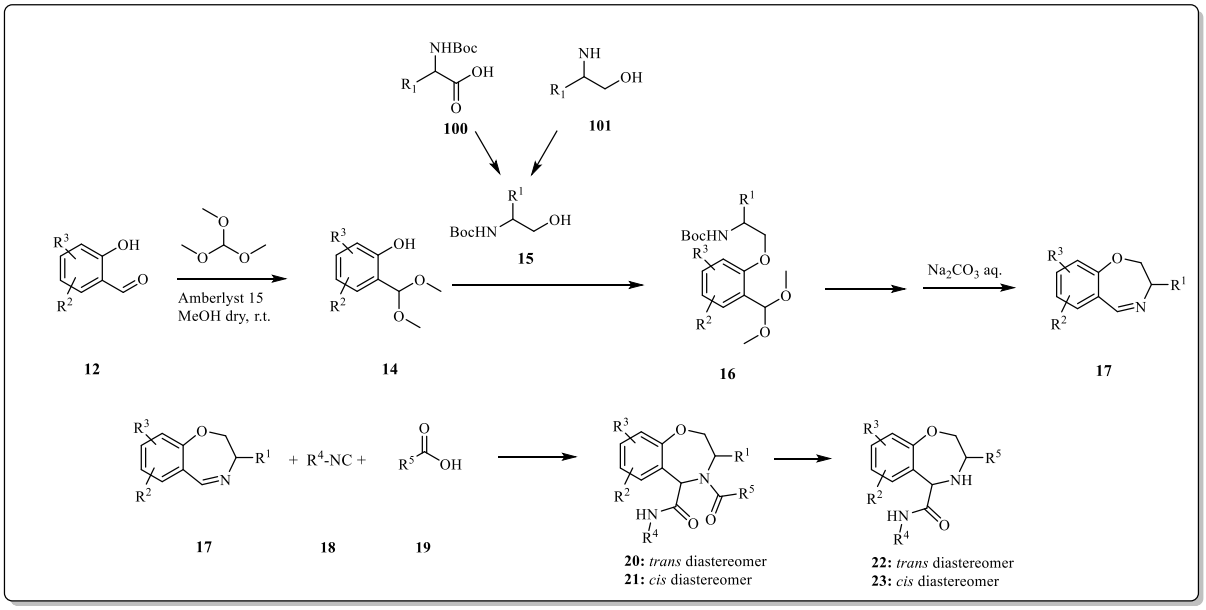
Using seven-membered cyclic imine **90** the multicomponent reaction afforded a good diastereoselectivity (up to 90:10 in favor of *cis* diastereomer). The mechanism depicted in Scheme 30 was used to explain this degree of stereoselectivity. Starting cyclic imine **90** is expected to prefer a half-chair conformation with the R^1 substituent in an equatorial position. Attack from the upper face leads to axial ion **94**, whereas attack from the lower face leads to equatorial ion **95**. Here the α-addition requires a prior conformational rearrangement which gives twist conformation **96**, in order to place the nitrilium ion in an axial position and avoid *peri* interactions. In **94**, there is not this problem, because the nitrilium ion is already in an axial position, and thus **97** is readily (and irreversibly) formed. Finally, O→N acyl migration gives the final *cis* adduct **93**. From an enthalpic point of view, both processes are feasible, but the need for a conformational rearrangement makes the route that leads to **93** *trans* less entropically favorable.



Scheme 30. Rationalization of observed diastereoselectivity.

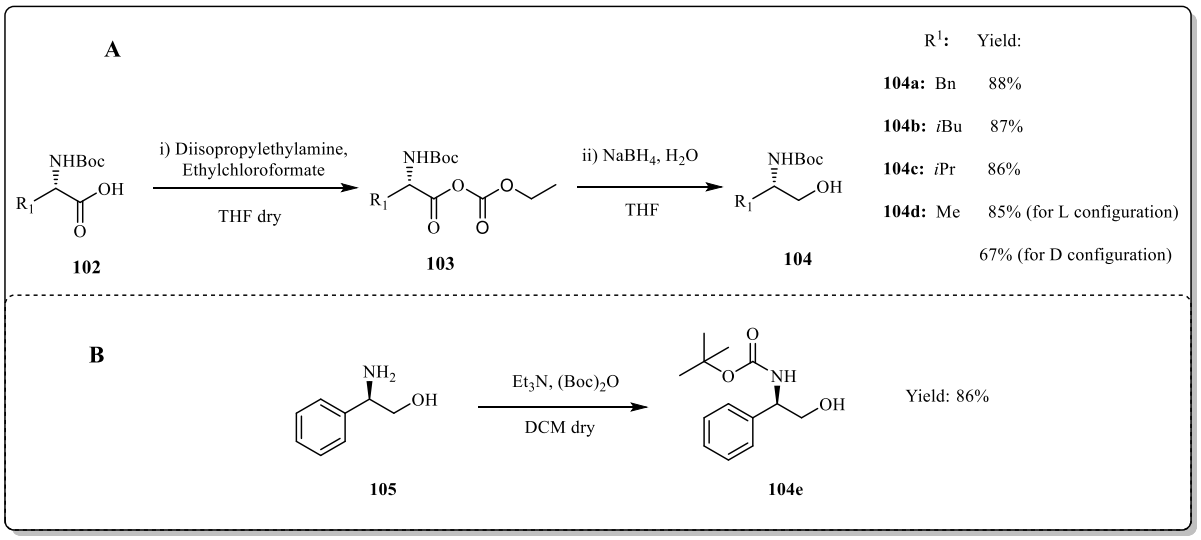
Having in hand an already optimized procedure including a very diastereoselective multicomponent process producing a specie with a tertiary amide that could be converted into a secondary amine giving a compound structurally far from classical proline-derived catalysts, the described method was chosen as starting point for my purpose.

Since it is also possible to obtain imines **90** in enantiomerically pure form, but the scarce availability of enantiopure amino-alcohols limits the generality, employing Boc-amino alcohols deriving from reduction of α-Boc-amino-acids **100** or protection of commercially available amino alcohols **101** was preferred (Scheme 31). As introduced in chapter 1, this strategy would increase the steric induction of the final potential catalyst producing two stereogenic centers close to the nitrogen atom.



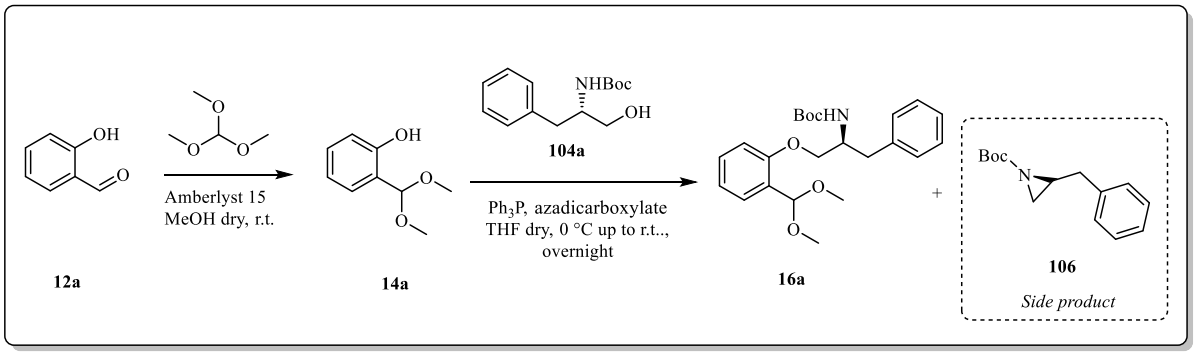
Scheme 31. Proposed strategy to obtain secondary amines.

The reduction of Boc-α-amino acids proceeds through the formation of a mixed anhydride **103** which is then reduced with $NaBH_4$ in the presence of water (Scheme 32, A). Alternatively, the product can be obtained by a simple introduction of the Boc-protecting group on the amino alcohol (Scheme 32, B).[63]



Scheme 32. Synthesis of Boc-amino-alcohols.

The Boc-amino-alcohol is then involved in a Mitsunobu reaction with the protected form of the salicyl aldehyde **12a** (Scheme 33), which has to be used as crude product because of its instability through chromatographic column. The reaction was immediately noted to be critical because of the tendency of **104** to give intramolecular cyclization. The known aziridine **106**[64] (Scheme 33) was indeed detected since the first test with TBAD as azadicarboxylate compound and **104a** as substrate (entry 1, Table 2).



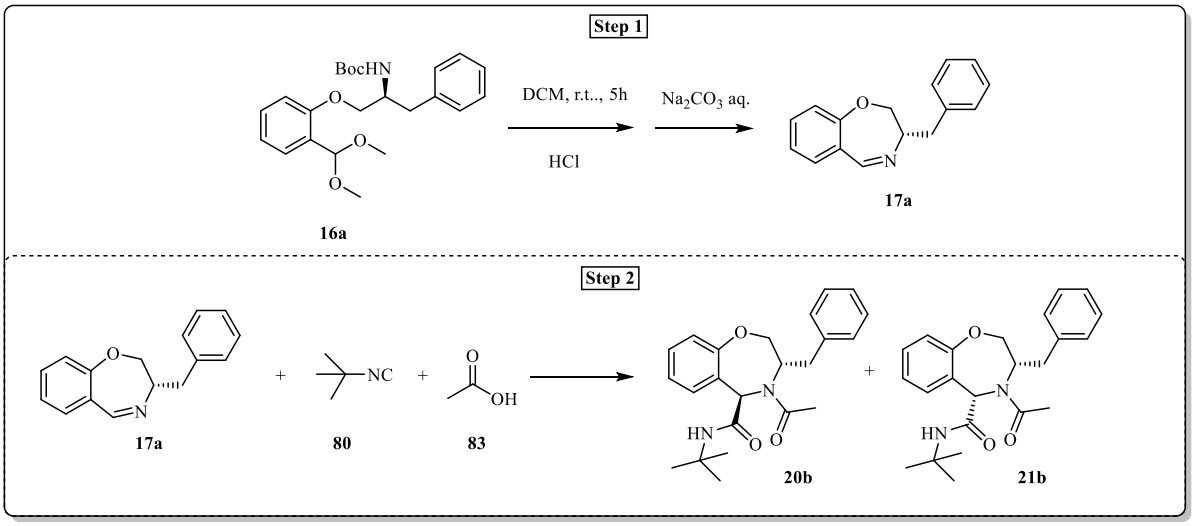
Scheme 33. Synthesis of Mitsunobu product **16a**.

An optimization of this reaction was thus necessary testing different aza-dicarboxylate compounds, such as DEAD and DIAD, but the yield remained unsatisfactory, due to the formation of substantial amounts of **106** (entries 2-3, Table 2). This result was not completely unexpected, taking into account some literature precedents on Mitsunobu reactions of phenols with this type of Boc-amino alcohols, where yields are often low and strongly depend on the nature of the starting phenol.[65,66] The intramolecular cyclization was mostly suppressed using ADDP.

Table 2. Optimization of Mitsunobu reaction.

Entry	Azodicarboxylate	Isolated yield (%) of 16a (from 14a)	Isolated yield (%) of 106 (from 14a)
1	Di-*tert*-butyl azodicarboxylate (TBAD)	25	54
2	Diethyl azodicarboxylate (DEAD)	45	31
3	Diisopropyl azodicarboxylate (DIAD)	31	44
4	1,1'-(Azodicarbonyl)dipiperidine (ADDP)	72	12

As described above, the Mitsunobu product can be very easily converted in the cyclic imine by acid catalyzed cleavage of Boc group and the acetal. The latter has to be used as crude product because of its instability on silica gel. Thus, all presented yields for the multicomponent reaction have been calculated on two steps. Cyclic imine **17a** was used to perform the optimization of the Ugi-Joullié reaction using ^{t}Butyl isocyanide and acetic acid (Scheme 34).



Scheme 34. Two step-procedure for the synthesis of **20b** and **21b**.

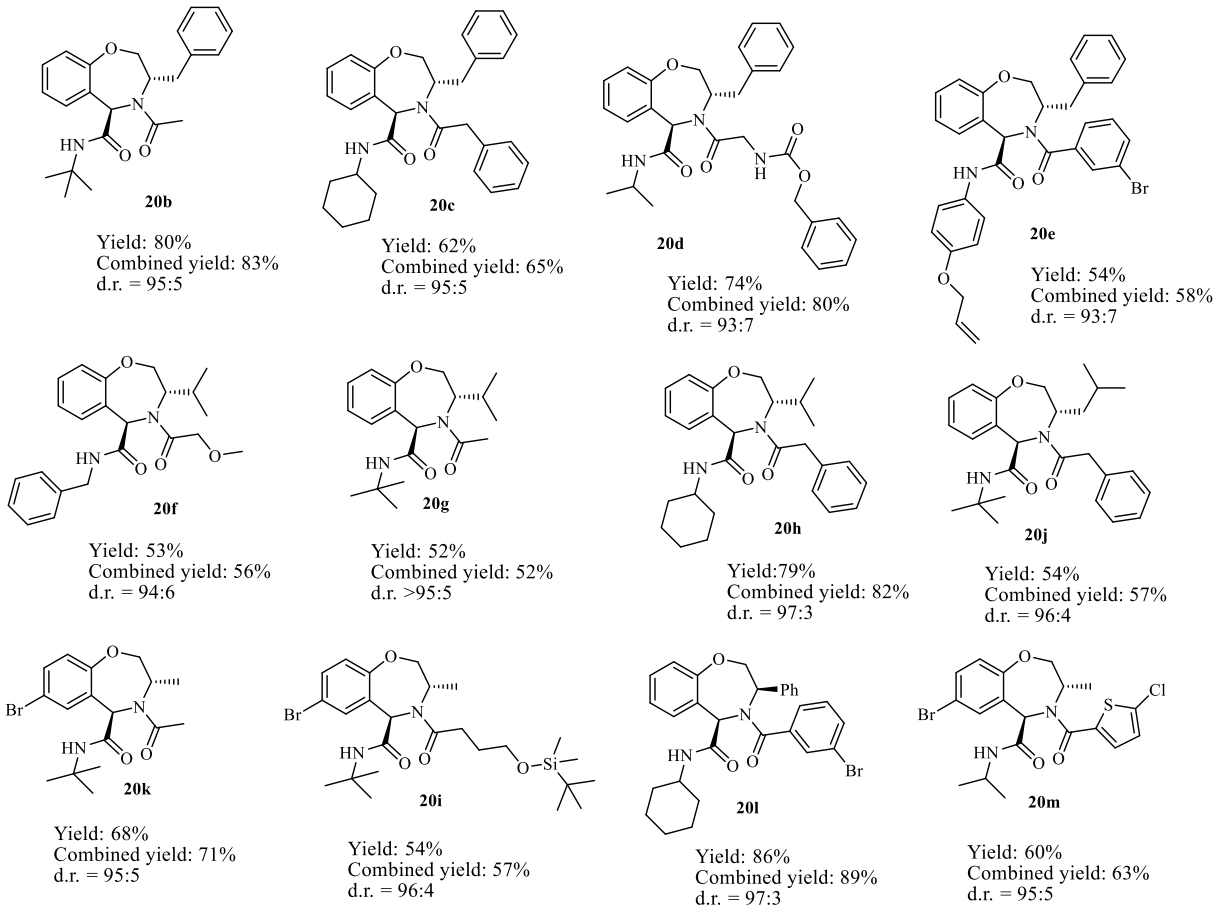
Different reaction conditions have been tested, but the best result was obtained in MeOH at room temperature for 45h (entry 1, Table 3).

Table 3. Optimization of Ugi-Joullié reaction.

Entry	Solvent	Additive	t	T (°C)	Yield (%)[a]	d.r.[b]
1	MeOH	none	45 h	r.t.	80	96 : 4
2	CH_2Cl_2	none	38 h	r.t.	74	90.5 : 9.5
3	CH_2Cl_2	$ZnBr_2$ (0.5 equiv.)	45 h	r.t.	69	94 : 6
4	CH_2Cl_2	$ZnBr_2$ (1.0 equiv.)	48 h (incomplete)	r.t.	51	89:11
5	MeOH	$ZnBr_2$ (0.5 equiv.)	48 h (incomplete)	r.t.	49	96 : 4
6	CH_2Cl_2	$Zn(OAc)_2$ (1.2 equiv.)[c]	48 h (largely incomplete)	r.t.	9	95 : 5
7	THF	none	48 h (incomplete)	r.t.	29	88 : 12
8	THF	$ZnBr_2$ (0.5 equiv.)	48 h (incomplete)	r.t.	34	95 : 5
9	THF	$Zn(OAc)_2$ (1.2 equiv.)[c]	48 h (no reaction)	r.t.	-	-
10	EtOH	none	48 h (incomplete)	r.t.	62	92 : 8

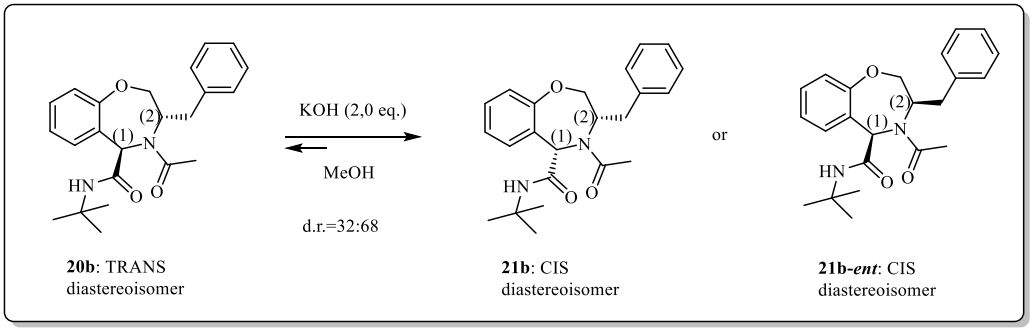
[a]Isolated yield of major diastereomer only. [b]Determined by HPLC on the crude product. [c]$Zn(OAc)_2$ was used instead of AcOH.

Moreover, the reaction showed a very high diastereoselectivity. The same result was obtained for all the reaction that I performed with different substrates (Scheme 35), so it demonstrates a high versatility of the reaction from this point of view. These results show also the wide range of enantiopure products that can be obtained simply varying the nature of the salicyladehyde, the amino alcohol, the carboxylic acid and the isocyanide. Finally, both enantiomeric series of tetrahydrobenzoxazepines are accessible, thanks to the easy availability of 1,2-amino-alcohols or α-amino acids in either enantiomeric forms.



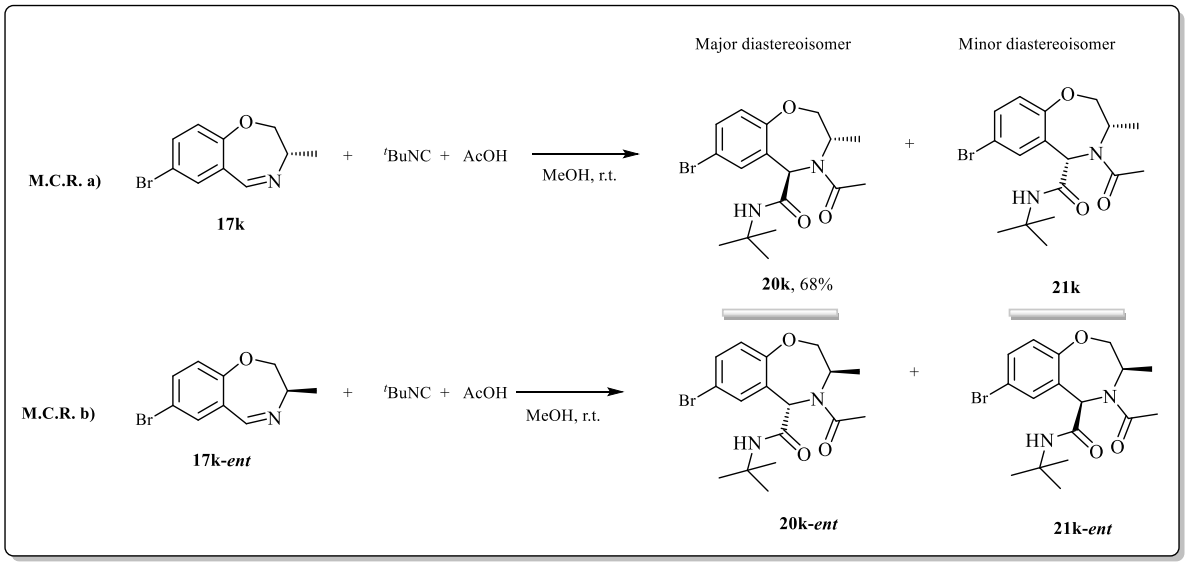
Scheme 35. Reaction scope.

At the beginning of the work, we thought that a truncated Ugi reaction was sufficient to get the free amine group. So, I performed the reaction involving the cyclic imine **17a**, *tert*-butyl isocyanide both with boric acid and zinc bromide, but in both cases I did not get any result. One more chance was to get the free amine through a hydrolysis reaction of the tertiary amide group. I involved the product **20b** in this test under basic conditions with KOH in MeOH. I did not get the desired product. What I obtained is an epimerization phenomenon giving a d.r. of 32:68. This is not what we expected to get, but it is a very important result. From this data we can understand that the major product of the multicomponent reaction is the kinetic diastereoisomer and not the thermodynamic one.



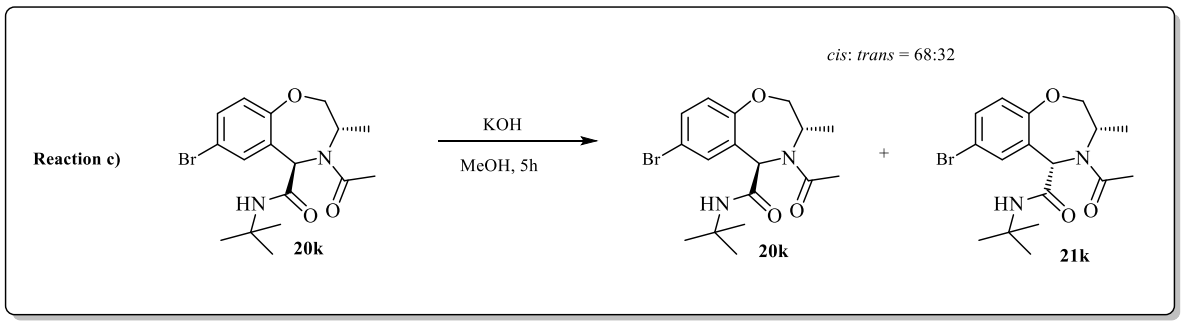
Scheme 36. Epimerization reaction.

Moreover, the diastereomeric ratio is the same also after 25h. This means that this is the value that we find when the equilibrium is established. If the chiral center where the epimerization occurs is (*1*) the *cis* diastereomer **21b** will be formed. If the epimerization occurs at the center (*2*) its enantiomeric form **21b-*ent*** will be produced (Scheme 36). The problem is that we are not able to understand which is the real product through a simple NMR. Obtaining the two couples of enantiomers, one for each diastereomer, was necessary. Two multicomponent reactions were, thus, performed (Scheme 37).



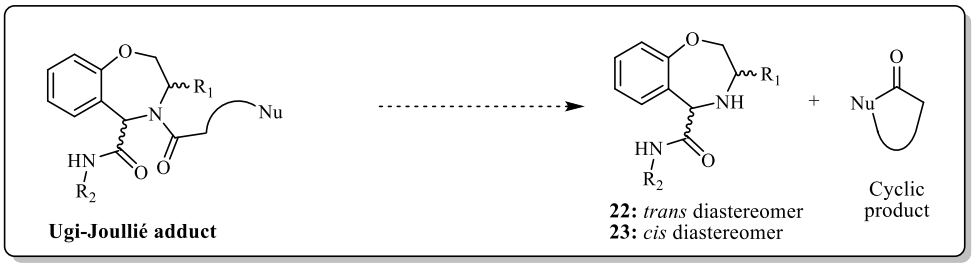
Scheme 37. Products of M.C.R. **a** and **b**.

We did not focus our attention on the yield of the reaction **b** because our interest was directed simply in the obtainment of products **20k-*ent*** and **21k-*ent*** to use them as reference on chiral HPLC analysis. A preparative TLC on part of the crude was sufficient to get them. I involved compound **20k** in the epimerization reaction (reaction **c**, Scheme 38) which produced a *cis*: *trans* ratio of 68:32 and comparing the analysis on chiral stationary phase of the two crudes (reactions **a** and **c**) showed that both **20k** and **21k** were enantiomerically pure and different from **20k-*ent*** and **21k-*ent***. This fact clearly demonstrates that epimerization occurs at center (*1*).



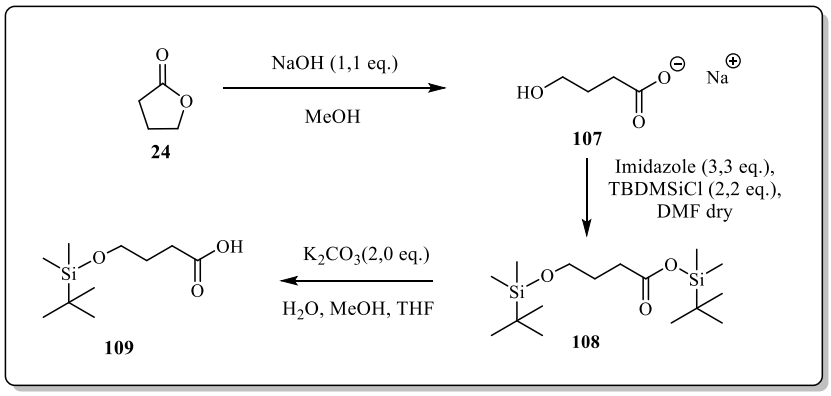
Scheme 38. Epimerization reaction.

If we obtain a Ugi-Joullié product endowed with an additional nucleophilic group, we will be able to look for the best reaction conditions useful to promote an intramolecular reaction that produces the cyclic product and the free amine group (Scheme 39).



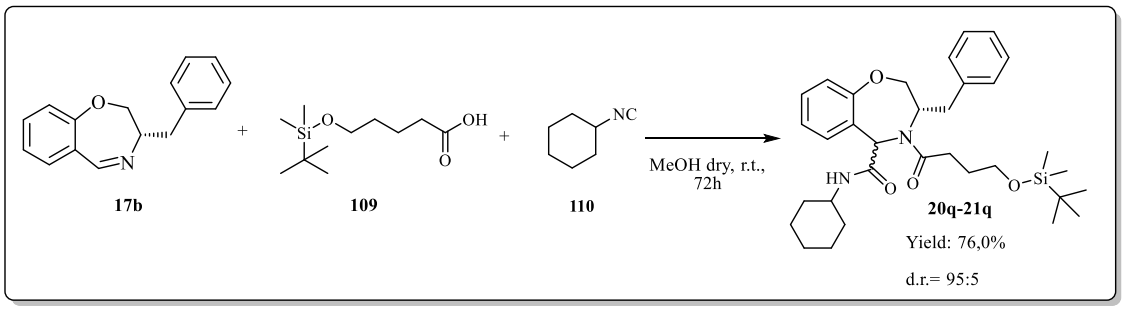
Scheme 39. Intramolecular cyclization reaction.

I started from the synthesis of the carboxylic acid **109** (Scheme 40). It is a three step procedure[67] that begins with the solvolysis of γ-butyrolactone **24** to form the sodium salt **107**. It is directly involved in the production of disilylate compound **108**. This step is quite critical due to the volatility of the product. An ice bath for evaporation of solvents under reduced pressure is required. Finally, the last step generates the desired acid which can be used as crude product since its NMR is quite clean.



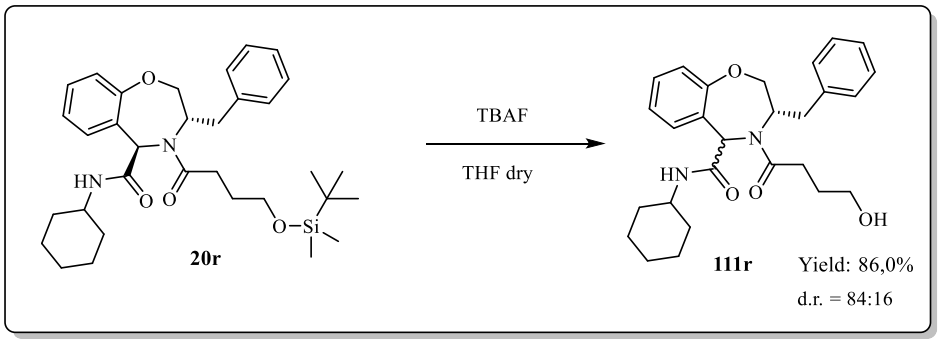
Scheme 40. Synthesis of carboxylic acid **109**

It was involved it in the Ugi-Jolullié reaction obtaining product **20q-21q** with high yields and high diastereoselectivity (Scheme 41).



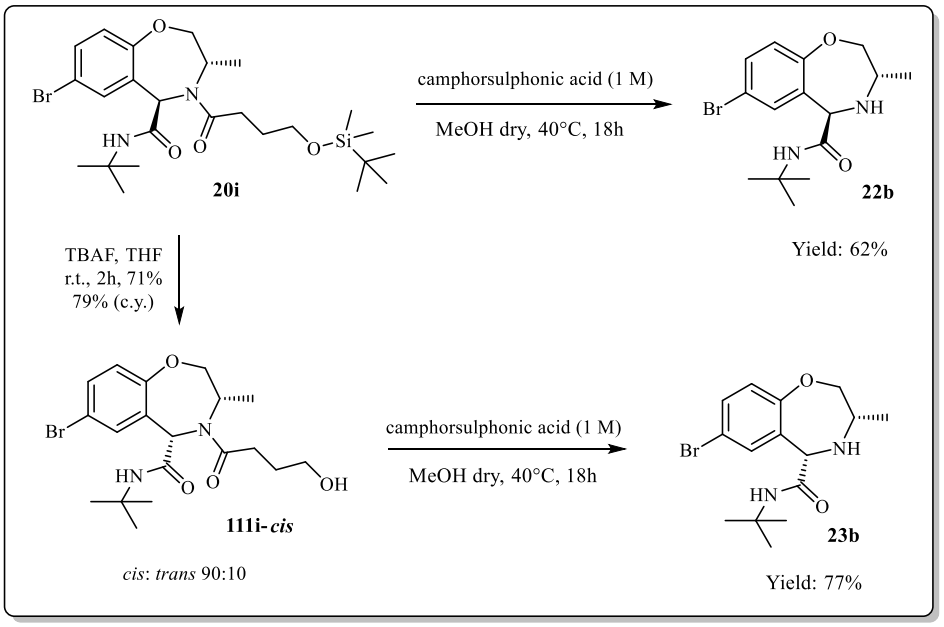
Scheme 41. Synthesis of the Ugi-Joullié product **20q-21q**.

I isolated the kinetic diastereomer and involved it in the classical conditions in order to promote the remotion of the silyl protecting group and the spontaneous intramolecular cyclization. I simply obtained the free alcohol group and, despite of the mild basic conditions, the epimerization phenomenon (Scheme 42).



Scheme 42. Deprotection of the alcohol group.

By treatment of **20i** with camphorsulphonic acid in MeOH the desilylation reaction takes place quickly without epimerization at r.t. Then, by raising the temperature to 40 °C the intramolecular nucleophilic attack leads to the release of γ-butyrolactone and to the formation of the diasteromerically pure **22b** (Scheme 43).



Scheme 43. Synthesis of the new potential organo-catalysts.

The same conditions convert *cis* alcohol **111i** to diastereomerically pure amine **23b**. Thus, thanks to the TBAF promoted epimerization, it is possible to stereodivergentely convert *trans* **20i** into both *trans* and *cis* amines **22b** and **23b**, depending on reaction conditions. Since both enantiomers of amino alcohols **104** are available, this means that all four stereoisomers of these secondary amines are easily accessible. This fact is quite useful in view of investigation of these secondary amines as organocatalysts: we can explore both decoration diversity (up to 3 diversity inputs) and stereochemical diversity. It is worth noting that amines **22b** and **23b** are completely stable against epimerization under basic conditions (TBAF or KOH), indicating that only *N*-acylated compounds are prone to epimerization.

The analysis of Ugi-Joullié products **20** is not so easy from the practical point of view because they give rotamers and this makes an analysis in DMSO-d_6 at high temperature necessary. With the products **22** and **23** the analysis is easier. Indeed, using $CDCl_3$ and room temperature is sufficient to have a clear spectrum. This is the reason why we waited for

obtaining the free amine to do NMR analysis to understand the relative configuration of these compounds. Through a NOESY-2D of product **23b** I observed the spatial correlation between H-5 and H-3, which can be present only in the *cis* compound. This correlation was not found in **22b**. We performed the following study using the commercial software ChemBio3D Ultra and the MOPAC (PM3) interface to have a conformational analysis of compounds **22b** and **23b** and confirm our hypothesis.

First, we have searched for all the local minima of the parent compound (Figure 4). This parent compound gives rise to three conformations with similar energy (Table 4). One of them resembles a chair, while the second one resembles a twist and the third one a boat. Thus, here we conventionally adopt these three terms. Obviously, each of these three conformations exist in two possible enantiomeric forms, which are in equilibrium. A notable difference between them is that in the chair and twist conformations the axial hydrogen at *C*-5 is located on the same side of the median plane than *C*-2 and *C*-3. On the contrary, in the boat, they are opposite.

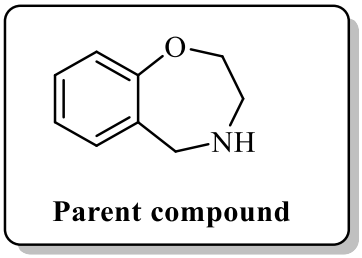
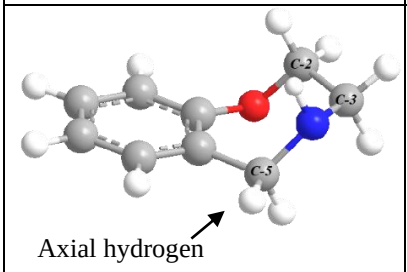
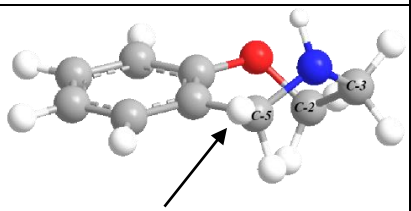
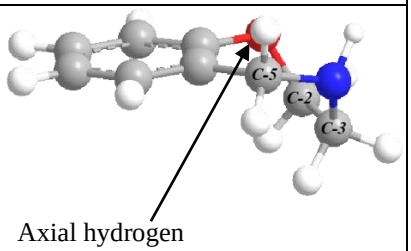


Figure 4. Parent compound used for conformational analysis.

Table 4. Conformational analysis of parent compound.

Chair	Twist	Boat
		

When passing to the real compound, the two conformations of each type become diastereomeric. Thus, we must consider 6 different conformations for each diastereomer. We have searched for the absolute minimum for each of them. According to the heat of formation found, the ones evidenced in yellow are more likely.

From these results, it is clear that in general, as expected, conformations that place H-3 and/or H-5 in axial position are favored. Obviously, this means that the substituents at C-5 and/or at C-3 are equatorial. Therefore, the lower energy is obtained for the chair conformation of the *cis* compound, where both hydrogens are axial (entry 2, Table 5).

In any case, the differences in heat of formation among the best three conformations of both isomers is too scarce to allow us to draw conclusion on the preferred one.

However, from the data in the tables, it is evident that no conformation of *trans* isomer may be able to give a NOE between H-3 and H-5 (Table 6). On the other side, the best three

conformations of *cis* compound can give it. We thus think that this is a proof of the stereochemical assignment.

Unfortunately, we are not able to measure precisely both J between H-3 and H-2, because one of the diastereotopic H-2 falls very near to H-3 in both isomers. These coupling constants could have given an useful information regarding the stereochemical equilibria, because, as can be seen from the tables, the dihedral angles are quite different among them.

Table 5. Conformational analysis of *cis* **21**.

.

Entry	**Type**	**Heat of formation (Kcal/mol)**	**Position of H-5**	**Position of H-3**	**Distance between H-5 and H-3 (Å)**	**Dihedral angles between H-2 and H-3**
1	Chair	-60.49	axial	axial	2.31	178, 61
2	Twist	-59.48	axial	axial	2.45	91, 29
3	Boat	-59.39	equatorial	axial	2.50	153, 32
4	Chair	-57.76	equatorial	equatorial	4.09	68, 52
5	Twist	-57.15	equatorial	equatorial	4.11	175, 55
6	Boat	is converted to other conformations	axial	equatorial	-	-

Table 6. Conformational analysis of *trans* **20**.

Number	Type	Heat of formation (Kcal/mol)	Position of H-5	Position of H-3	Distance between H-5 and H-3 (Å)	Dihedral angles between H-2 and H-3
1	Chair	-60.06	equatorial	axial	3.61	67, 53
2	Chair	-59.79	axial	equatorial	3.68	174, 65
3	Twist	-59.55	axial	equatorial	3.61	149, 28
4	Twist	-58.73	equatorial	axial	3.73	97, 24
5	Boat	is converted to other conformations	axial	axial	-	-
6	Boat	is converted to other conformations	equatorial	equatorial	-	-

On these bases, it can be noted that the kinetic diastereomer of the multicomponent reaction is the *trans*-specie. The diasteroselectivity of the reaction towards this diastereomer can be explained considering that imine **17** exists in just two half-chair conformations depicted in Figure 5. The one on the left has the methyl substituent in axial position. The conformation on the right is more stable by about 0.80 Kcal/mol, according to MOPAC–PM3. In both conformations the C=N bond is coplanar to the benzene ring, and the face *trans* to the substituent is less hindered.

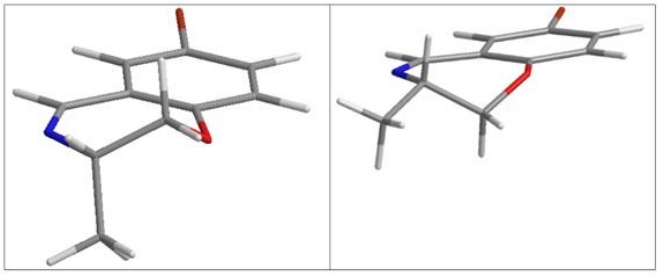
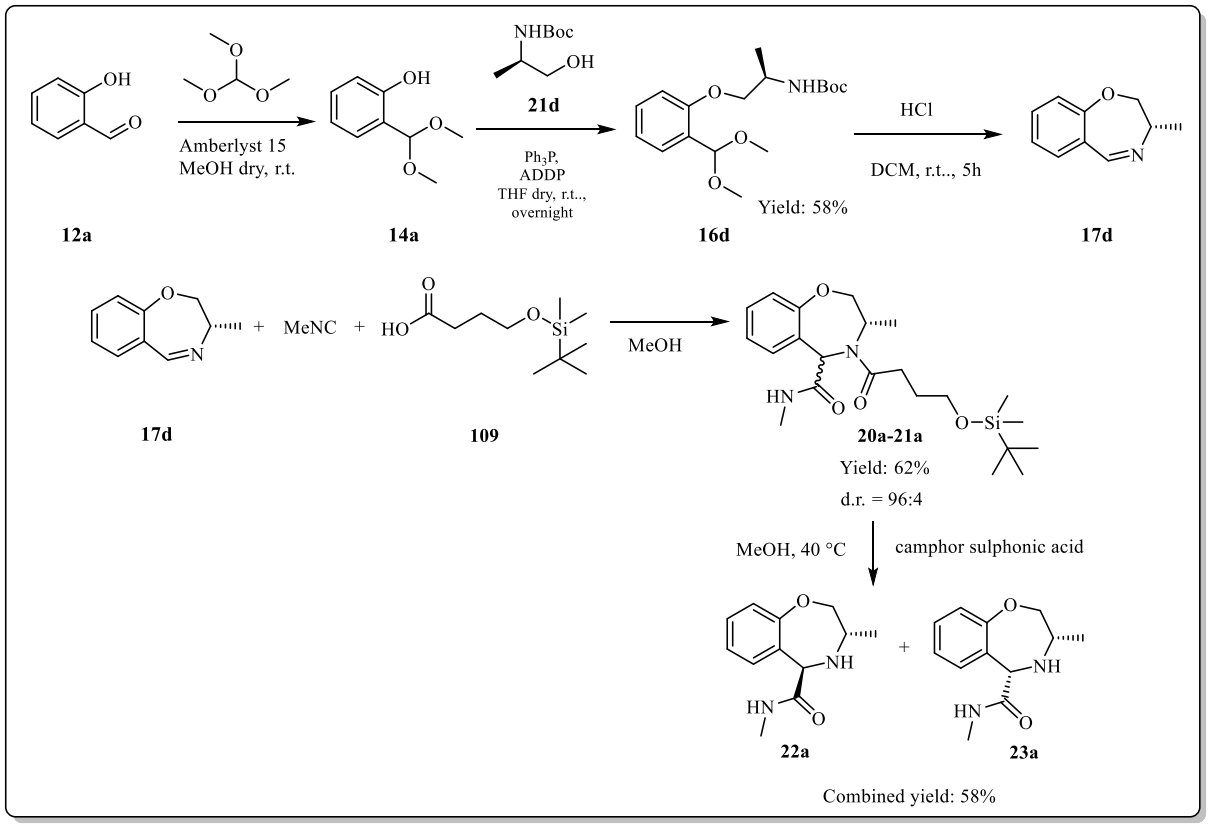


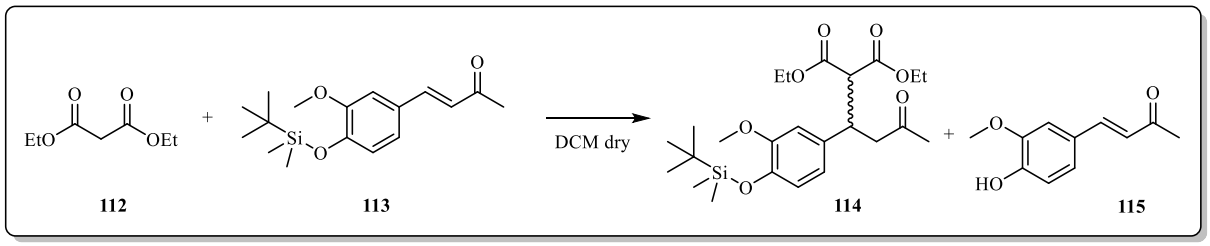
Figure 5. Conformations of cyclic imine.

The less sterically hindered and structurally complex compound **22a** was chosen as first potential organo-catalyst to be tested. It was prepared following the optimized procedure. The Ugi-Joullié reaction (Scheme 44, it has to be performed at to 40 °C in order to be complete after 72h) gave product **20a-21a** as a mixture of diastereomers not easily separable through chromatographic column. Thus, they have been involved together in the final step to obtain the desired product, whose *trans* diastereomer of **22a** could be isolated.



Scheme 44. Synthetic strategy which was used to obtain a new potential chiral organo-catalyst.

The first approach to the study of the catalytic activity of **22a** regarded the asymmetric synthesis of product **114** through Michael reaction between diethylmalonate **112** and the α,β-unsaturated ketone derived from vanillin, previously protected with TBDMSiCl (**113**, Scheme 45). This, in order to use substrates derived from biomasses.



Scheme 45. Michael reaction for catalysis' tests. **113** and **112** (2.0 eq.) were dissolved in the solvent (0.25M), at r.t. and the reaction progress was followed by TLC.

First, the reaction was performed without any kind of catalyst or additive to verify that it cannot occur spontaneously (entry 1, Table 7). The reaction proceeded slowly using pyrrolidine (Figure 6) as catalyst, but it produced **114** (entry 2, Table 7) in a sufficient amount to be used as reference for the determination of *e.e*. from chiral-HPLC analysis. The desired product was isolated through a preparative TLC on a small amount of the crude product without determining the yield of reaction. Et_3N was used as reference to compare the time of reaction with **22a**, involved in a parallel reaction (entry 3-4, Table 7). My compound did not show any catalytic activity and, although Et_3N was expected to give base catalysis, it simply produced **115**. The same result was obtained with DBU, which brought the reaction to completeness in four days (entry 7, Table 7) and also it was able to suppress the catalytic

effect of pyrrolidine when the two species have been combined to favor the deprotonation of **112** and, thus, the catalytic activity of pyrrolidine (entry 8, Table 7). The absence of catalysis with **22a** could be explained by a missing formation of the iminium ion which could be favored with an acid catalysis (Scheme 16) or base catalysis. The latter should promote the deprotonation of malonate and the release of the proton which is necessary for the iminium ion formation. Using AcOH (Figure 6) no results were obtained (entry 5, Table 7). When adding together **22a** and DBU (Figure 6) the reaction produced **115** more slowly (entry 9, Table 7). This suggests some interaction between my compound and the base, but it was no longer investigated. Both Et_3N and pyrrolidine have been investigated as bases when combined with **22a**. While the first gave again the same result (entry 6, Table 7), increasing the amount of pyrrolidine simply favored its catalytic activity, as expected.

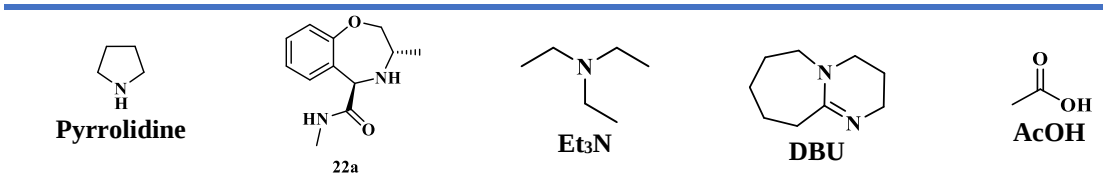


Figure 6. Molecules tested as catalysts or additive in Michael reaction.

Table 7. First approaches to the evaluation of catalytic activity of **22a** in Michael reactions.

Entry	Catalyst (20 mol%)	Additive	t (days)	Product
1	/	/	10	/
2	Pyrrolidine	/	10	**114** (reaction not complete)
3	**22a**	/	10	/
4	Et_3N	/	10	**115** (reaction not complete)
5	**22a**	AcOH (20 mol%)	1	/
6	**22a**	Et_3N (20 mol%)	1	**115** (reaction not complete)
7	/	DBU (1.1 eq.)	4	**115** (reaction complete)
8	Pyrrolidine	DBU (1.1 eq.)	4	**115** (reaction complete)
9	**22a**	DBU (1.1 eq.)	4	**115** (reaction not complete)
10	**22a**	Pyrrolidine (1.1 eq.)	4	**114** (reaction complete)

The reaction progress was followed by TLC.

Du and co-workers reported the use of **116** as catalyst in Michael reactions, supposing a participation of the tosyl group in the activation of the malonate (Figure 7).[68]

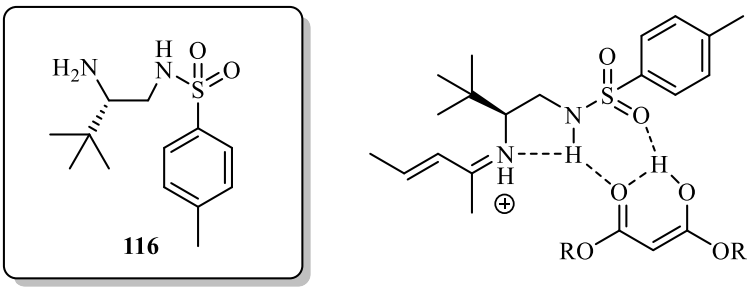
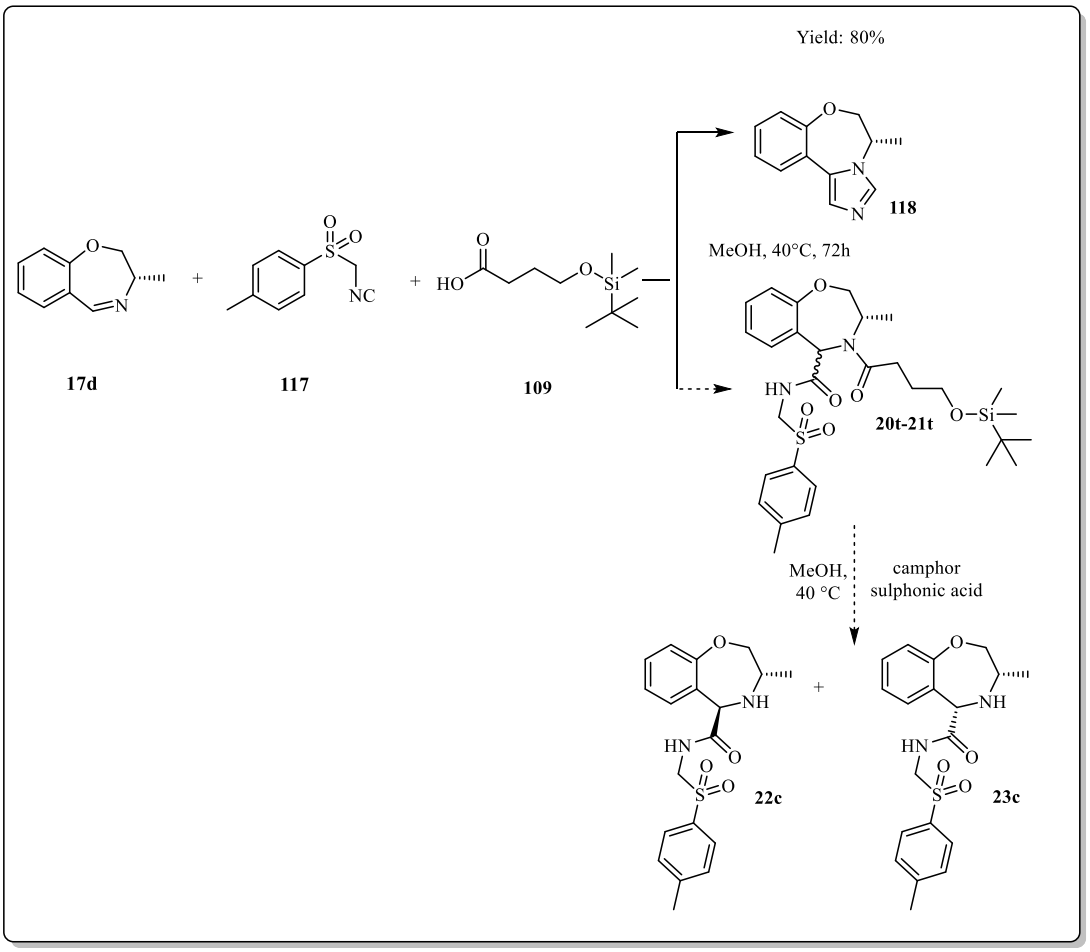


Figure 7. Du and co-worker's catalyst (on the left) and the activation mode of Michael reaction (on the right).

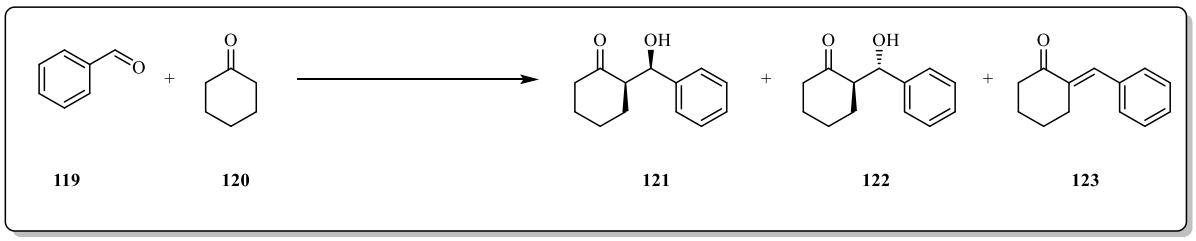
Inspired from this structure, Tosyl methyl isocyanide **117** was involved in the multicomponent reaction in order to obtain **20t-21t** and convert them in the final product **22c-23c** (Scheme 46). The reaction was performed at 40 °C based on the results obtained for similar reactions. Unexpectedly it produced the van Leusen product **118** as major compound.[69] How the reaction conditions influenced this outcome was no longer investigated.



Scheme 46. Synthetic strategy which was used to obtain the potential chiral organo-catalyst **22c-23c**.

Thus, we decided to test the catalytic activity of **22a** in aldol reactions. Cossìo and co-workers reported the use of compound **124** and several similar compounds as catalysts for the aldol

reaction between benzaldehyde **119** derivatives and cycloexanone **120** (Scheme 47).[54] Through a collaboration between Prof. Cossìo's group and mine, we have been asked to test my compounds in the same reaction.



Scheme 47. Aldol reaction between benzaldehyde and cycloexanone.

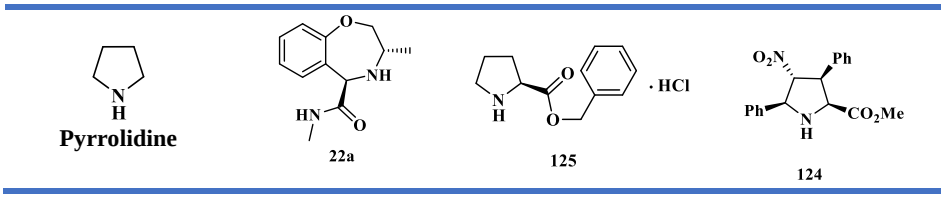


Figure 8. Molecules tested as catalysts in aldol reaction.

First, the reaction was performed only with TFA as additive to qualitatively value the rate of reaction without any catalyst (entry 1, Table 8).

Table 8. First approaches to the evaluation of catalytic activity of **22a** in aldol reaction.

Entry	Catalyst (30 mol%)	Additive	Solvent	T (°C)	t	Product
1[a]	/	TFA (30 mol %)	neat	r.t.	8 days	**121** and **122** (reaction not complete)
2[a]	Pyrrolidine	TFA (30 mol %)	neat	r.t.	8 days	**121**and **122** (reaction not complete)
3[a]	**22a**	TFA (30 mol %)	neat	r.t.	8 days	/
4[a]	**22a**	TFA (15 mol %)	neat	r.t.	8 days	/
5[a]	**22a**	AcOH (30 mol %)	neat	r.t.	8 days	/
6[b]	Pyrrolidine	TFA (30 mol %)	CH_3CN	r.t.	7 days	**123** (reaction not complete)
7[b]	Pyrrolidine	TFA (15 mol %)	CH_3CN	r.t.	7 days	**123** (reaction not complete)
8[b]	Pyrrolidine	TFA (46 mol %)	CH_3CN	r.t.	7 days	**123** (reaction not complete)
9[b]	Pyrrolidine	TFA (30 mol %)	CH_3CN (with 1% of H_2O)	r.t.	7 days	**123** (reaction not complete)

10	Pyrrolidine	TFA (15 mol %)	CH_3CN (with 1% of H_2O)	r.t.	7 days	**123** (reaction not complete)
11[b]	Pyrrolidine	TFA (46 mol %)	CH_3CN (with 1% of H_2O)	r.t.	7 days	**123** (reaction not complete)
12[c]	**124**	TFA (30 mol %)	neat	r.t.	20 h	**121** and **122** (reaction complete)
13[c]	Pyrrolidine	TFA (30 mol %)	neat	r.t.	20 h	**121** and **122** (reaction not complete)
14[c]	**22a**	TFA (30 mol %)	neat	r.t. up to 60 °C	4 days	**121** and **122** (reaction not complete)
15[c]	**22a**	TFA (15 mol %)	neat	60 °C	3 days	**121** and **122** (reaction not complete)
16[c]	**125**	/	neat	r.t. up to 60 °C	4 days	**121**, **122** and **123** (reaction not complete)

[a]The reaction was performed in neat **120** with a **120**/**119** ratio of 60:1. [b]The reaction was performed in the solvent (0.5 M) with a **120**/**119** ratio of 2:1. [c]The reaction was performed in neat **120** with a **120**/**119** (freshly distilled) ratio of 60:1. All the reactions progress were followed by TLC.

It proceeded effectively more slowly than the reaction performed with pyrrolidine (entry 2, Table 8), but in both cases the products were observed just in traces through TLC. Using **22a** no product was observed (entry 3, Table 8), suggesting a protonation of the amine group by the acid. The same result was obtained with a lower concentration of TFA and a milder acid like AcOH (entry 4-5, Table 8). Thus, other reaction conditions were tested with pyrrolidine as catalyst. The reaction resulted to be sensitive to acetonitrile producing **123** as major product (entry 6-11, Table 8). It was partly isolated from other side products without determining the yield of reaction, since we were only interested to understand the type of molecule produced by the reaction. At this point we realized that these preliminary tests gave results not easily rationalized because of impurities contained in the reagents, mainly in cycloexanone that was used in excess. Thus, I performed the next tests on freshly distilled substrates. Reproducing Cossìo and co-workers' reaction conditions with **124** (Figure 8) in its racemic form allowed me to obtain **121** and **122** (entry 12, Table 8). They were partly isolated from the other side products, in order to have the two NMR- and HPLC-references. Surprisingly pyrrolidine showed a much lower catalytic efficiency, compared with bulkier **124**. On the other hand our amine **22a** was able to produce traces of the desired products (entry 14, Table 8). I tried to determinate the degree of conversion through an NMR analysis of the crude product, using tetrachloro-3-nitrobenzene as internal standard, but the conversion was too low to be determined. Proline benzyl-ester **125** (Figure 8) was tested as catalyst to compare qualitatively the rate of reaction with pyrrolidine and value the effect of an ester group on the catalytic activity. The only difference between the two catalysts regarded the obtainment of **123** as additional product, with the use of **125** (entry 16, Table 8). In this case, however the catalyst was poorly soluble.

In conclusion, starting from enantiomerically pure Boc-amino alcohols chiral cyclic imines **17** can be obtained. This kind of substrates give rise to a very diastereoselective multicomponent reaction. The two diastereomers can be separated through a simple

chromatographic column, which is not common for this kind of reactions. More important, we showed that multicomponent processes can be involved in an efficient synthetic pathway to obtain new potential organo-catalysts, which can be obtained in both the diastereomeric forms despite of the high diastereoselectivity of the MCR and are stable against the epimerization phenomenon. First approaches to the study on the catalytic activity of secondary amines like **22a** in Michael and aldol reactions did not bring about the desired results. Different additives have been used, in order to favor the formation of enamine or iminium ion which were necessary for catalysis, but the reactions did not show improvements. More studies are necessary to understand the parameters that may favor the desired catalysis. Other reaction conditions and structures similar to **22a** have to be tested.

2.4. *N*- *vs* O-Glycosylations

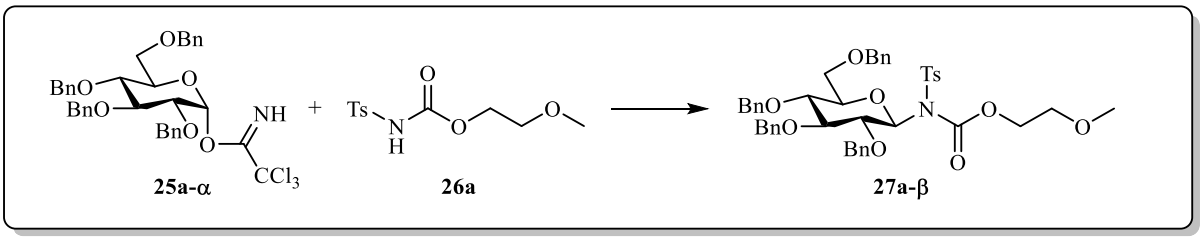
2.4.1 Erasmus+ Mobility for Traineeship

At the beginning of my third year of Ph.D. I was involved in an Erasmus program that allowed me to spend six months at the University of Copenhagen under the supervision of prof. Christian Marcus Pedersen. His research is focused on carbohydrates chemistry and glycosylation reactions.

2.4.2 Glycosylation reactions

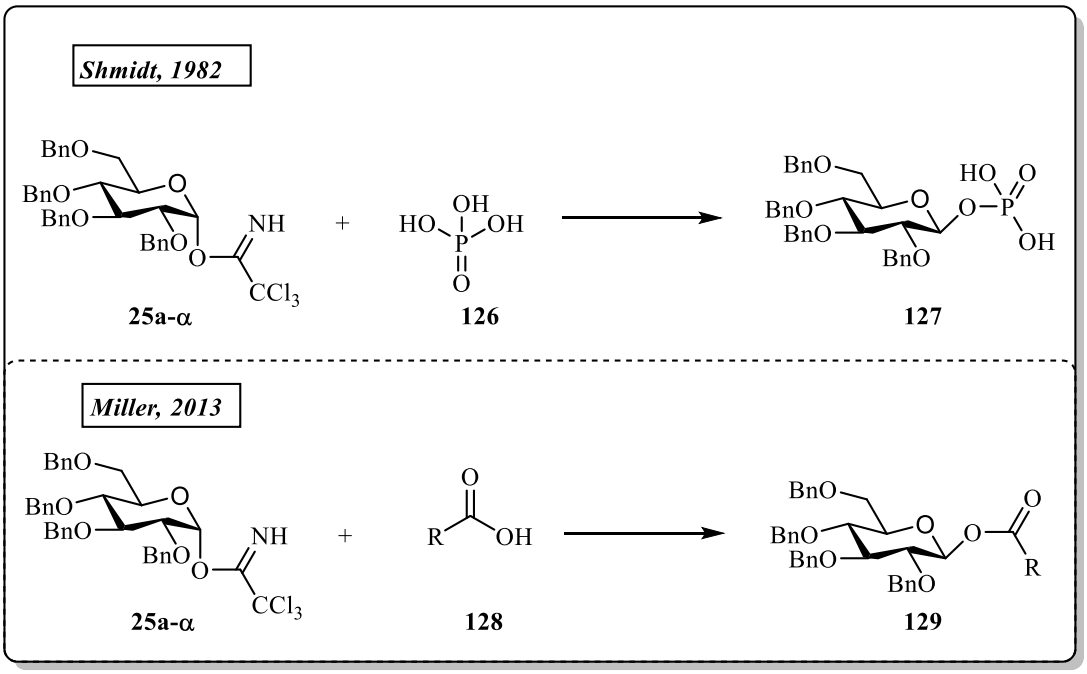
Glycosylation reactions are the most famous process in carbohydrate chemistry.[18,70-72] They involve a glycosyl donor (electrophile), which must be activated, and a glycosyl acceptor (nucleophile).[73] Based on what type of acceptor is involved, different kind of glycosyl bond can be formed.[74-79] Among them, the *O*- and *N*-glycosyl bonds are of particular interest and hence received much attention.[80-82] *O*-glycosides are omnipresent with different functions and relevance from a biological point of view.[73] *N*-glycosylation is crucial in post-translational modifications, where monosaccharides are connected to proteins *via* a glycosyl amide bond linkage.[81-83] Other biologically active *N*-glycosides, like *N*-glycosyl sulfonamides, have recently received attention. These can be obtained *via* an addition of sulfamides to acetyl-protected glycals (*via* Ferrier rearrangement) or from monosaccharides, both in the presence of boron trifluoride etherate.[84,85] Some of these compounds have been found to be carbonic anhydrase (CA) inhibitors.[15,85,86] The same biological activity has been shown by *O*-glycosides containing aromatic sulfonamide residues.[87-89] A different synthetic pathway was developed for this type of compounds. Indeed, a 1,3-dipolar cycloaddition reaction was used in order to generate 1,4-disubstituted 1,2,3-triazole glycoconjugate sulfonamides from alkyne-substituted sugars and azido aromatic sulfonamides.[87,88] Due to the importance of these kind of *N*- and *O*-glycosides, the development of a single simple method able to bring both *N*- and *O*-glycosyl bonds is highly important.

Recently, the research group of prof. Pedersen reported that sulfonamides react with trichloroacetimidates (TCAs) in a stereospecific and self-promoted manner forming *N*-glycosides (Scheme 48).[15]



Scheme 48. Self-promoted *N*-glycosylations.

Self-promoted reactions are processes that can be activated by one of the involved reagents without using external catalysts or additives.[16,17] The work reported by Pedersen is not the first example of self-promoted glycosylation. Shmidt *et al.* reported that in some cases carboxylic acids and phosphorous acid derivatives can activate the α-trichloroacetimidates to promote a glycosylation with inversion of stereochemistry (Scheme 49).[90] This inversion was explained by pre-complexation of the TCA donor and acid, leading to a pseudo six-membered transition state[91] and a concerted mechanism, without the formation of an oxocarbenium intermediate. The Miller group even showed that a wide range of carboxylic acids can act as catalytic activators of TCA donors and the catalytic efficiency of these catalysts is inversely proportional to their pKa-value. Carboxylic acids with higher pKa-values simply resulted in self-condensation of the catalyst and TCA donor, thus yielding undesired glycosyl esters.



Scheme 49. Self-promoted *O*-glycosylations.

Even the *N*-glycosylation reported by the Pedersen group proceeds as a self-promoted process thanks to acidity of the acceptor that, in this case, is the sulfonamide specie **26**. The acid character, which was noted in many species used as acceptors (Figure 9) makes the sulfonamide functionality able to activate TCA donors with a subsequent nucleophilic attack to the glycosyl cation (Scheme 50) *i.e.* they act as both catalysts and nucleophiles (glycosyl acceptors).

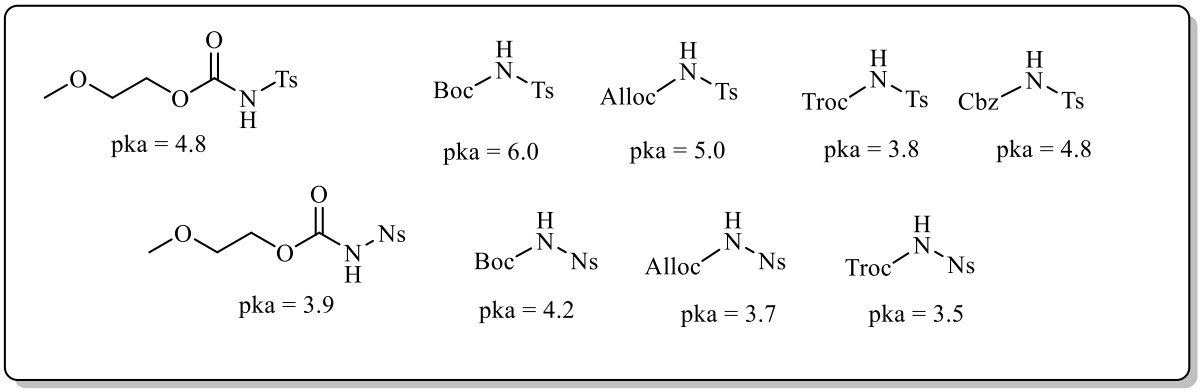
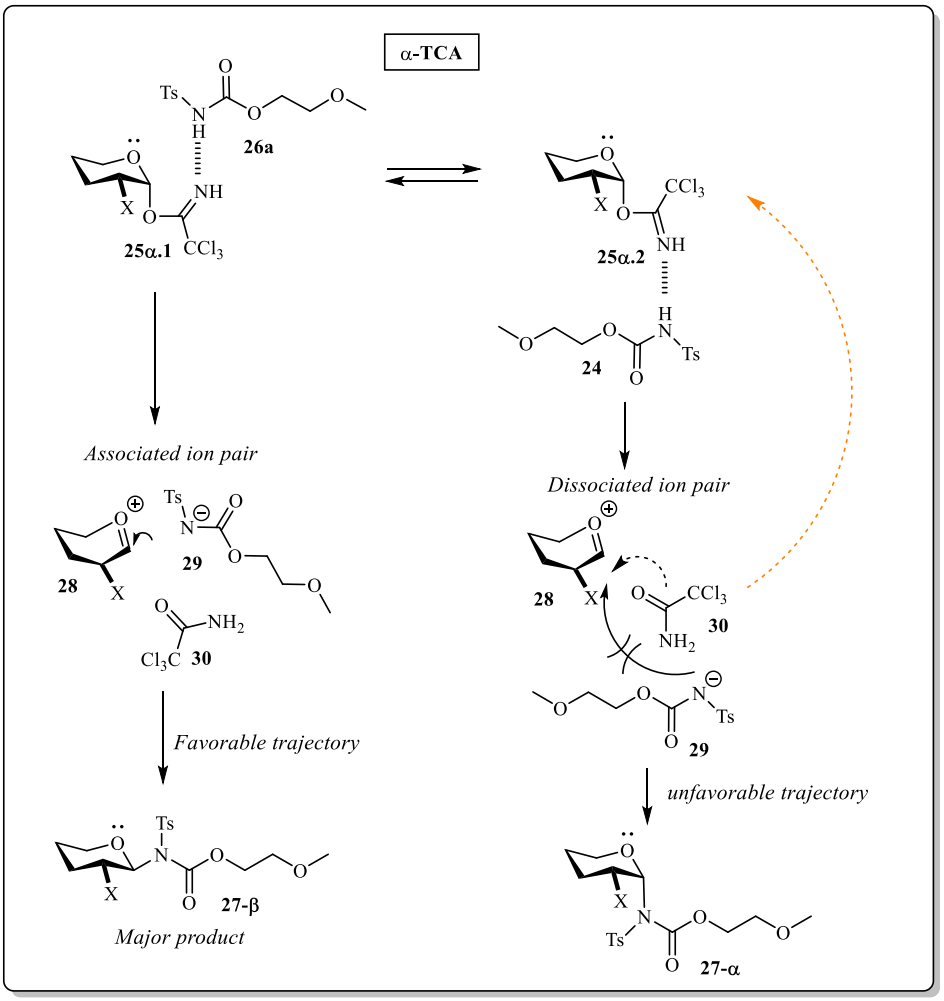


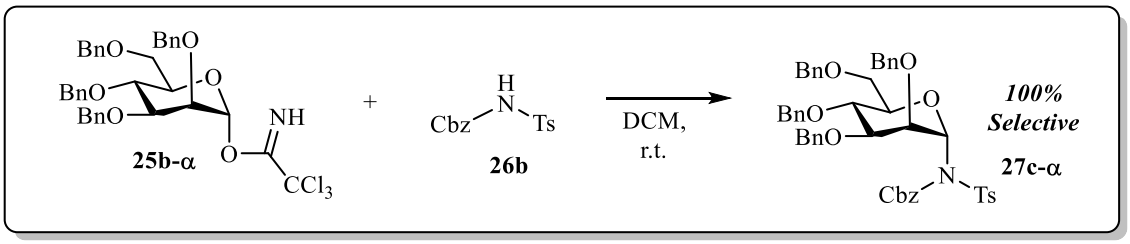
Figure 9. Sulfonamides used in previous work.

The reactions have been found to be highly stereospecific with inversion of configuration, which is very useful as TCAs often can be synthesized in a stereoselective manner.[92] One can thereby determine the *N*-glycoside stereochemistry already when synthesizing the glycosyl donor. In the preceding work, it was also realized that the degree of stereospecificity was dependent on the anomeric configuration. Axial TCAs often resulted in high equatorial selectivity, whereas using equatorial TCA the same degree of stereoselectivity was not always observed. This difference in selectivity, when using the preferred solvent for glycosylation (DCM), was explained by two mechanistic pathways. The activation of the glycosyl donor can either lead to the formation of an associated or dissociated ion pair. When the TCA is axially oriented (Scheme 50), the donor exists as two different conformers, which **25α.1** has previously been found to be energetically favorable.[91] Upon activation an associated and a dissociated ion pair can be formed. In the first one the amide ion **29** is in close proximity to the glycosyl cation intermediate **28** and should thus react more readily to form the β-anomer of the product. On the other side, the nucleophile attack in the dissociated ion pair is blocked by the C-2 substituent. Also, the back reaction to form the TCA donor could be a competing reaction (orange dotted arrow). This can explain such a high preference for the formation of 1,2-transglycosides that was found for both the gluco and galacto α-TCA donors.



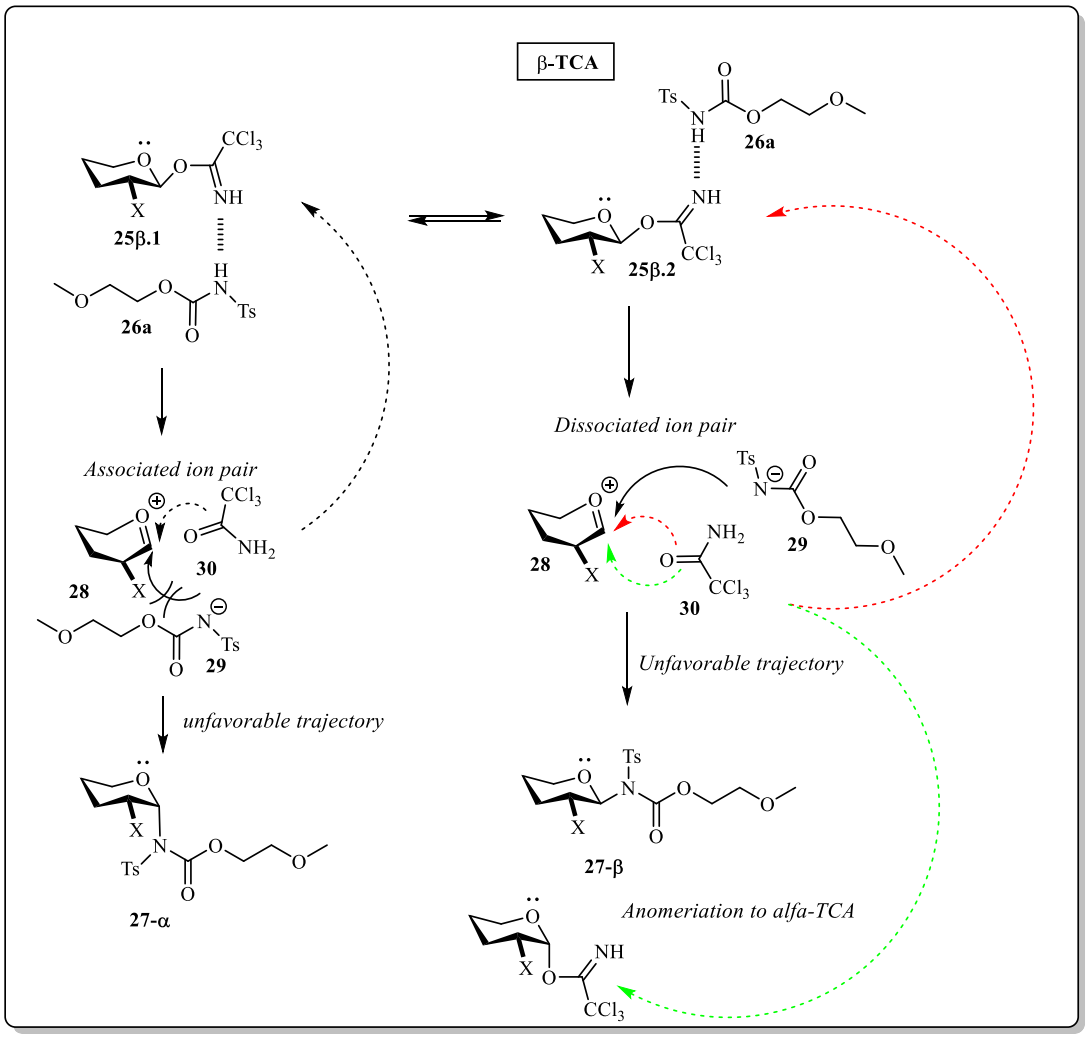
Scheme 50. Proposed mechanism for self-promoted *N*-glycosylation reactions using axial TCAs.

Even using manno-derived donors 1,2-*trans*-glycosides are obtained (Scheme 51), as the associated ion pair is obscured by the axial C-2 substituent. Thus, the dissociated ion pair is made the more favorable intermediate leading to the α-anomer of the product.



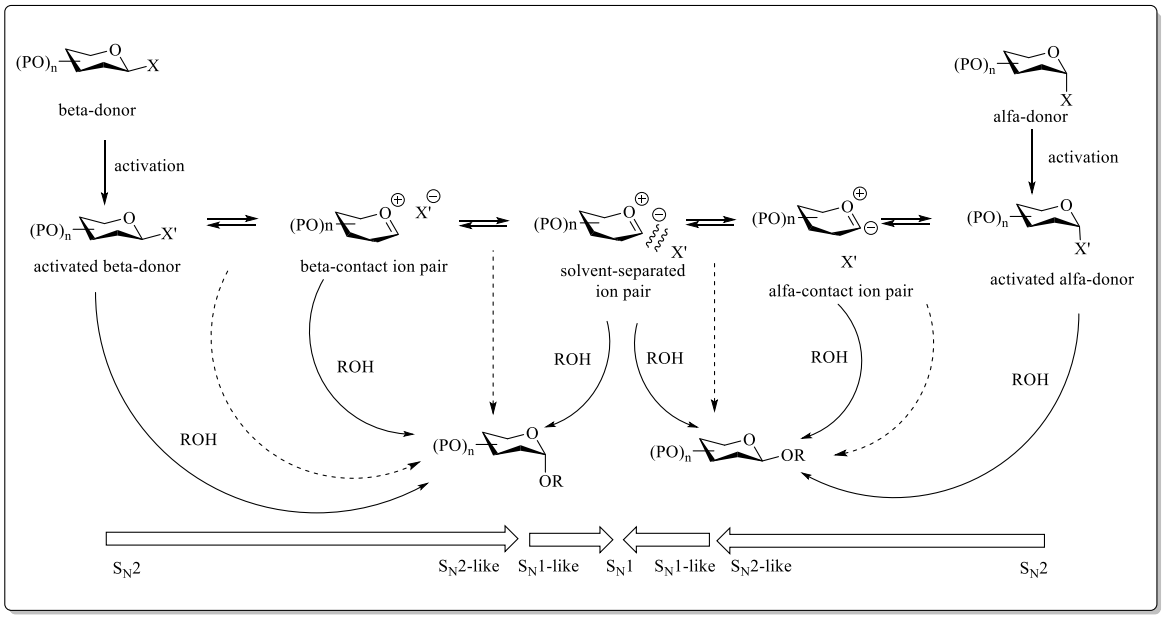
Scheme 51. Self-promoted *N*-glycosylation using manno-derived TCA.

With activated and substituted equatorial (β)-TCAs the associated ion pair is no more so favorable since the C-2 substituent of the pyranose ring will block the trajectory of the incoming nucleophile and, thus, a more dissociative reaction path is followed. The nucleophilic attack is however sterically hindered by the leaving group **30** (Scheme 52). Consequently, this can lead to *in situ* anomerisation (Scheme 52 in green and red), resulting in formation of the α-TCA, with a consecutive loss of stereochemical information from the glycosyl donor and hence a mixture of products.[15]



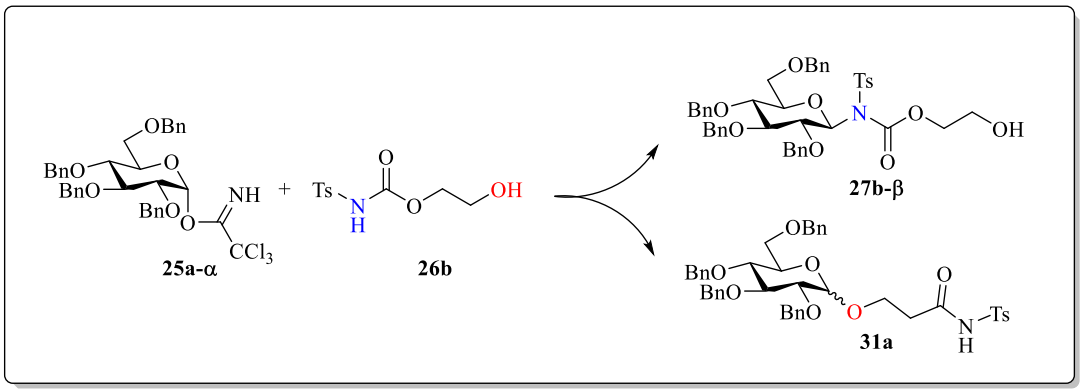
Scheme 52. Proposed mechanism for self-promoted *N*-glycosylation reactions using equatorial TCAs.

Contact and solvent-separated ion pairs are on the borderline between a S_N1 and a S_N2 mechanism. Small changes in the reaction condition can therefore shift the balance to either site. Important parameters in this aren *e.g.* the polarity of the solvent and its ability to promote a charge separation (Scheme 53).[18-20] The dissociative reaction path allows two competing reaction pathways resulting in low anomeric selectivity.



Scheme 53. Contact and solvent-system separated ion pairs involved in a continuum glycosylation mechanism.

My work was aimed to better understand the reaction mechanism that involves sulfonamides as acceptors and how it is influenced by the reaction conditions. An alcoholic function was inserted in the acceptor with this purpose (Scheme 54). The nucleophilic attack from this group would be favored only by the formation of dissociated ion pairs. On the other side *N*-glycosylation is favored with a more associative mechanism. Thus, simply valuing the *N*-glycoside: *O*-glycoside ratio it is possible to understand the favored mechanism involved in the reaction.



Scheme 54. *N*- vs *O*-glycosylation in self-promoted processes.

Trichloroacetimidates are one of the most used glycosyl donor types. They are prepared under basic conditions, starting from the hemiacetal. Depending on the conditions and the stereochemistry of the starting sugar, especially at C-2, mainly the α- or β-anomer can be obtained.[15,92] My study primary involved the thermodynamically more stable axial TCA (α) as this gives raise to the equatorial product in the glycosylation and has a greater stability.

The perbenzylated glucopyranosyl trichloroacetimidate **25a-α** was synthesized as a glycosyl donor model and 2-hydroxyethyl tosylcarbamate **26b** was used as a glycosyl acceptor model (Scheme54).[15] This acceptor contains both a primary alcohol and a

sulfonamide, but only the latter can activate the TCA. As the reaction is self-promoted only the two reactants and solvent are present, hence ruling out effects of metals ions, counterions and consequently reduce the complexity significantly.

Initially, the reactions were performed in DCM as this is the most commonly used solvent for glycosylations. Glycosylating **26b** gave, as expected, a mixture of *O*- and *N*-glycosides. The *N*-glycosylation was very selective towards the β-product **27b-β** in line with earlier work (associative mechanism).[15] The *O*-glycoside **31a** on the other hand were found to be a 1:1 mixture suggesting a reaction presumably proceeding through a highly reactive glycosyl cation (dissociative mechanism). The products **27b-β** and **31a** have been isolated in order to be used as references for the determination of product ratios from crude-NMR. The isolated yields (34 % for *N*-glycoside and 40 % for *O*-glycoside) were found to be in accordance with the ratio obtained from crude NMR. With DCM as a reference point, other solvents were then used to study the effects of polarity and solvent properties. Interestingly, a change in the chemoselectivity was observed going from the least polar solvent in the study, toluene (entry 1, Table 9) to the most polar $MeNO_2$ (entry 4, Table 9). The difference in ratio is going from very *N*-selective to *O*-selective, but without a change in the anomeric selectivity of the *O*-glycosides, which also seems unaffected when using a participating solvent like THF.

Table 9. Effect of the increasing polarity of the solvent.

Entry	**25a-α** [M]	**26b** [M]	Solvent	*N*- vs *O*-glycosides
1[a]	0.073	0.110	PhMe	87:13
2	0.073	0.110	DCM	46:54
3	0.073	0.110	THF	56:44
4	0.073	0.110	$MeNO_2$	0:100

The donor and acceptor were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. [a] Performed at 40˚C. The data reported were determined through ^{1}H-NMR of the crude product.

When increasing the charge separation by using more polar solvents, the hydroxy group competes with the amide being the negatively charged counterion. In more polar solvents, the reaction is consequently shifted towards the O-glycosylation (dissociative mechanism). In less polar solvent like DCM there is less charge separation and the reaction results in both *N*- and *O*-glycosides. With the reaction on the borderline between mechanistic pathways it was expected that the concentration would also influence the reaction outcome. Therefore, the change of concentration of the sulfonamide was studied in both toluene and DCM (Table 10).

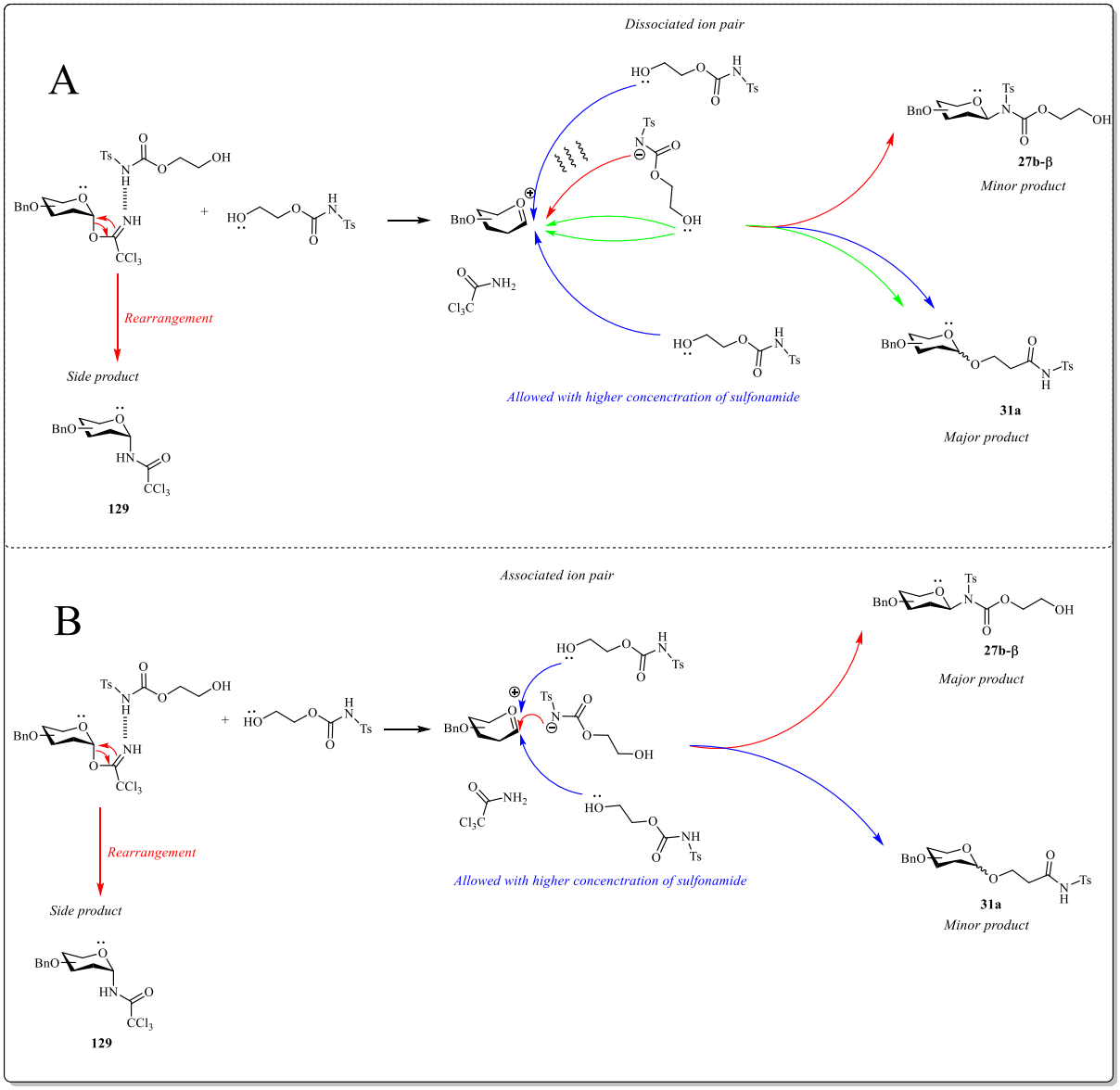
Increasing the concentration of the acceptor without changing the concentration of **25a-α** resulted in a decrease in *N*-selectivity in DCM (Table 10). This change in reaction outcome can be explained by a second molecule of **26b** attacking the dissociated ion pair resulting in more *O*-glycoside. This also explains why only a small excess of **26b** is sufficient to get a change in the chemoselectivity (entry 7 and 8, Table 10).

Table 10. Effect of changing the concentration of sulphonamide **26b**.

Entry	**25a-α** [M]	**26b** [M]	Solvent	*N*- vs *O*-glycosides	**129** (%)
1[a]	0.073	0.0146	PhMe	100:0	37
2[a]	0.073	0.049	PhMe	85:15	14
3[a]	0.073	0.110	PhMe	87:13	/
4[a]	0.073	0.367	PhMe	47:53	34
5	0.073	0.0146	DCM	70:30	30
6	0.073	0.049	DCM	70:30	/
7	0.073	0.091	DCM	60:40	/
8	0.073	0.110	DCM	46:54	/
9	0.073	0.367	DCM	14:86	19

The donor and acceptor were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. [a]Performed at 40˚C. The data reported were determined through ^{1}H-NMR of the crude product.

A different trend was observed in toluene (entry 3, Table 10). The low polarity of the solvent resulted in a decrease of the rate of reaction and therefore the reaction temperature was increased to 40 °C in order to be complete within 48 hours. The increase of temperature has no effect on the ratio between *N*- and *O*-glycosylation. Because of the lower solvent polarity, the ion pairs are tighter and the reaction with the alcohol is less competitive. The slow conversion of the sulfonamide to its dissociated form combined with the activation mode, based on a pre-complexation, ensures the presence of **26b** upon activation, with a consecutive intermolecular competition from the free alcohol giving the *O*-glycosylation (Scheme 55), even if it is not predominant (entry 2 and 3, Table 10). Sub-stoichiometric amounts of the acceptor are therefore required, in order to get a more selective *N*-glycosylation as a bimolecular (H-bond complex) reaction is favored and a termolecular reaction unlikely (entry 1, Table 10). A rearrangement of α-TCA donor can compete in the reaction (Scheme 52), producing the glucosyl trichloroacetamide **25a-α** as side product, both with high and low concentration of **26b** (Table 10). The participation of a second molecule **26b** was also supported by the results obtained when increasing the concentration of the reaction both in toluene and DCM, where more of the *O*-glycoside formed. A different trend was found in toluene. Its low polarity makes the rate of dissociation depending on the concentration of reaction. Thus, the more the reaction is diluted the more the conversion of the acceptor to its dissociated form is underdog. This results in a major concentration of **26b** giving *O*-glycosylation (Table 11).



Scheme 55. Proposed mechanisms for *N*- and *O*-glycosylation.

Table 11. Effect of changing the concentration of the reaction keeping the ratios constant.

Entry	**25a-α** [M]	**26b** [M]	Solvent	*N*- vs *O*-glycosides
1[a]	0.146	0.220	PhMe	83:17
2[a]	0.073	0.110	PhMe	87:13
3[a]	0.0146	0.022	PhMe	75:25
4	0.146	0.220	DCM	27:73
5	0.073	0.110	DCM	46:54
6	0.0146	0.022	DCM	56:44

The donor and acceptor were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. [a]Performed at 40˚C. The data reported were determined through ^{1}H-NMR of the crude product.

To study the effect of other counterions, in the self-promoted glycosylation, lithium salts were added. It has earlier been demonstrated that counterions influences the outcome of glycosylations and also that the Lewis acidity of Li^+ is enough to activate a TCA.[93,94]Using **25a-α**, 20 mol% of TfOLi or Tf_2NLi and **26b** in DCM completely changed the chemoselectivity and only the *O*-glycoside was observed (Table 12). Thus, the salt can change the reaction course of the self-promoted chemoselective glycosylation resembling a common acid catalyzed *O*-glycosylation.[93] The *O*-glycoside **31a** was obtained as a 1:1 mixture as the major product suggesting a dissociated mechanism.

Table 12. Effect of adding lithium salts.

Entry	Catalyst	Acceptor	N- vs O-glycosides
1	TfOLi	24	0:100
2	Tf_2NLi	24	0:100

The donor **1** (0.073 M) and acceptor (0.110 M) were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. The data reported were determined through ^{1}H-NMR of the crude product.

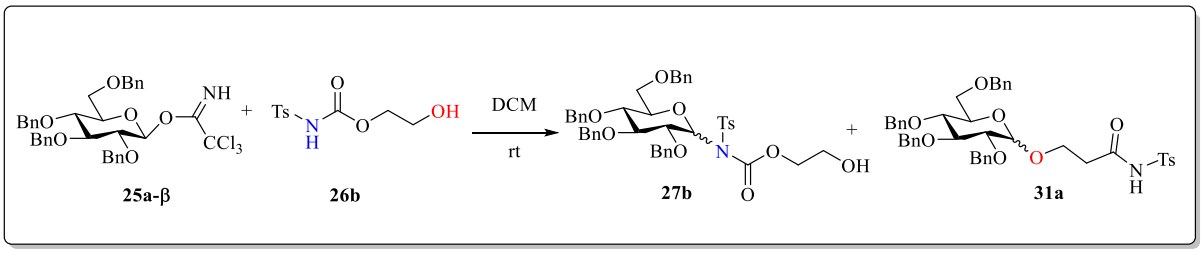
When performing the same reaction, without sulfonamide present, but with EtOH as the glycosyl acceptor, a similar stereoselectivity was obtained, suggesting that the sulfonamide is not participating in the activation when lithium salts are present (Table 13).

Table 13. Effect of adding lithium salts.

Entry	Catalyst	Acceptor	α : β product
3	TfOLi	EtOH	56:44
4	Tf_2NLi	EtOH	25:75
5	/	EtOH	/

The donor **23** (0.073 M) and acceptor (0.110 M) were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. The data reported were determined through ^{1}H-NMR of the crude product.

As described above, β-TCA donors often give rise to a mixture of anomers. When mixing **25a-β** and **26b** in DCM, a 40:60 mixture of α- and β-*N*-glycosides was obtained confirming that the reaction proceeds through a less associated reaction pathway and therefore gives lower selectivity (Scheme 56). Furthermore, it was noticed that the α-*N*-glycosides decomposed on the silica column biasing the product ratio (Table 14).



Scheme 56. Self-promoted glycosylation using the β-TCA **25a-β** and **26b**. A mixture of anomers of *N*-glycosides was obtained and the α-*N*-glycosides was found to be unstable upon purification.

Table 14 *N*- vs. *O*-glycosylation with β-TCA.

Entry	*N*- vs *O*-glycosides	α:β (3)	α:β (4)
1 (Before column)	100:0	40:60	/
2 (After column)	60:40	70:30	3:1

The donor **25a-β** (0.073 M) and acceptor (0.110 M) were dissolved in the solvent at r.t. and the reaction progress was followed by TLC. The data reported were determined through ^{1}H-NMR

Thus, we have demonstrated that the self-promoted *N*-glycosylation of sulfonamides takes place in a concerted manner and presumably through an activated H-bond complex. When increasing the amount of the sulfonamide a competing reaction pathway involving another molecule of the sulfonamide results in the formation of *O*-glycosides. The same effect can be obtained by adding lithium salts, which acts as both acid and nucleophilic catalysts, forming an intermediate glycosyl triflate. Consequently, all stereochemical information is lost. As the reaction is on the borderline between mechanisms, solvents influence the outcome dramatically. Apolar solvents favors tight ion pair leading to an associative mechanism, *i.e.* S_N2-type, whereas polar solvents lead to a dissociative mechanism closer to the S_N1 mechanism. Chemoselectivity and to some extent the stereoselectivity can be controlled by tuning the parameters.

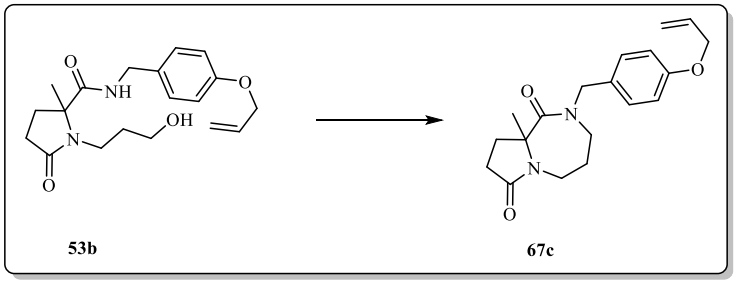
3. EXPERIMENTAL PROCEDURES

3.1 General experimental details

NMR spectra were taken at the indicated temperature in $CDCl_3$ or DMSO-d_6 at 300 MHz (^1H), and 75 MHz (^{13}C), using, as internal standard, TMS (^1H NMR: 0.000 ppm) or the central peak of $CDCl_3$ (^{13}C: 77.02 ppm), or the central peak of DMSO (^1H NMR DMSO-d_6; 2.506 ppm), or the central peak of DMSO (^{13}C in DMSO-d_6; 39.43 ppm). Chemical shifts are reported in ppm (δ scale). Peak assignments were made with the aid of gCOSY and gHSQC experiments. HRMS: samples were analysed with a Synapt G2 QToF mass spectrometer. MS signals were acquired from 50 to 1200 m/z in ESI positive ionization mode. TLC analyses were carried out on silica gel plates and viewed at UV (254 nm) and developed with Hanessian stain (dipping into a solution of $(NH_4)_4MoO_4$•4 H_2O (21 g) and $Ce(SO_4)_2$•4 H_2O (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming) or with ninhydrin. R_f were measured after an elution of 7-9 cm. Column chromatographies were done with the "flash" methodology using 220-400 mesh silica. Petroleum ether (40-60 °C) is abbreviated as PE. In extractive work-up, aqueous solutions were always reextracted three times with the appropriate organic solvent. Organic extracts were always dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions using dry solvents were carried out under a nitrogen atmosphere.

3.2 Bicyclic Heterocycles from Levulinic Acid

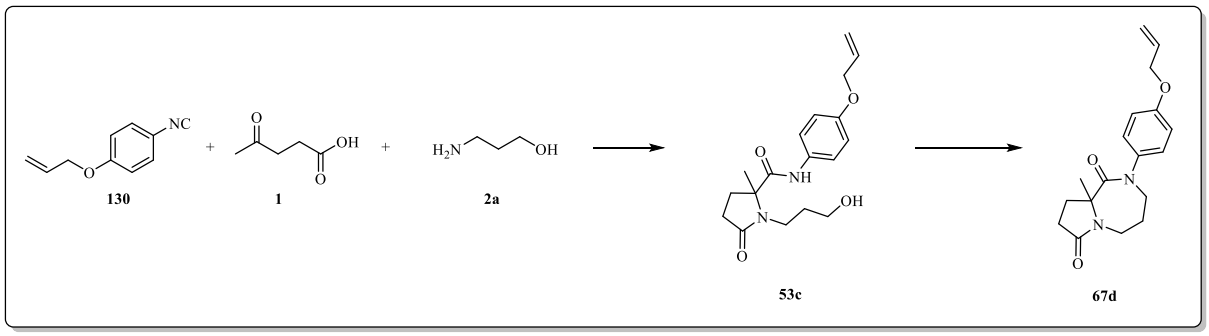
Synthesis of (*R*,*S*)-2-[(4-Allyloxyphenyl)methyl]-9a-methylhexahydro-1Hpyrrolo[1,2-a][1,4]diazepine-1,7(8H)-dione (67c):



A solution of Ugi adduct **53b** (2.0622 g, 5.95 mmol) in dry CH_2Cl_2 (60 mL) was cooled to –15 °C, and treated with triethylamine.(1.82 mL, 13.1 mmol) and with methanesulfonyl chloride (552 μL, 7.14 mmol). After 2h Et_3N (0.5 mL, 3.57mmol) and MsCl (0.14 mL, 1.7 mmol) were added. After 1h the reaction was complete by TLC. The mixture was poured into a 3:1 mixture of saturated aqueous NH_4Cl and 5 % aqueous $(NH_4)_2PO_4$, and extracted with AcOEt (pH of aqueous phase = 4). After evaporation to dryness, the crude mesylate was taken up in dry DMF (2.5 mL), and treated with NaH (60 % in mineral oil, 358.9 mg, 5.95 mmol). The solution was stirred at 50 °C overnight. Then it was poured into saturated NH_4Cl and extracted with AcOEt. Evaporation and chromatography (AcOET to AcOEt/MeOH, 95:5) gave pure **67c** (1.3824 g, 71 %). Oil. R_f = 0.24 (AcOEt). ^1H NMR (300 MHz, $CDCl_3$, 25 °C) δ 7.13 (d, J= 8.6 Hz, H meta to OAll, 2 H) 6.86 (d, J= 8.6 Hz, H ortho to OAll, 2H), 6.05 (ddt, J= 5.3, 10.5, 17.2 Hz, C*H*=CH_2, 1H), 5.41 (dq, J= 1.6, J= 17.2 Hz, CH=C*H*H, 1H), 5.28 (dq, J= 1.4, 10.5 Hz, CH=C*H*H, 1 H), 4.56 and 4.48 (AB syst, J= 14.4 Hz, Ar*CH_2*, 2H), 4.52 (dt,

J= 1.5, 5.3 Hz, *CH*$_2$CH=CH2, 2H) 4.16 (dt, J= 6.8, 13.8 Hz, H-5, 1H), 3.32 and 3.23 [ABXY syst, J= 14.7, 6.4 (ax), 9.5 (bx), 2.4 (ay = by) Hz, H-3, 2H), 2.97–2.77 (m, 2 H, H-5 and H-9), 2.39 (dd, J= 6.7, 8.7 Hz, H-8, 2H); 2.00–1.63 (m, H-9 and H-4, 3H), 1.59 (s, CH_3, 3H) ppm. ^{13}C NMR (75 MHz, CDCl3, 25 °C)δ 174.7, 174.2 (C=O), 158.1, 129.4 (quat,), 133.1 (*C*H=CH$_2$), 129.2 (C meta to OAll), 117.7 (CH=*C*H$_2$), 114.9 (C ortho to OAll), 68.8 (*C*CH$_3$), 67.6 (C-9a), 52.9 (N-*C*H$_2$Ar), 46.1 (C-3), 36.6 (C-5), 33.7 (C-9) 29.6 (C-8), 26.9 (C-4), 23.3 (CH3) ppm. GC–MS: Rt 11.08 min. M/z: 328 (M+. 10.6), 287 (5.7), 181 (100.0), 162 (6.4), 147 (62.9), 138 (10.3), 124 (12.1), 111 (16.7), 110 (12.7), 107 (9.9), 98 (17.8), 82 (8.4), 78 (5.7), 56 (42.3), 55 (23.2), 42 (17.3), 41 (65.2). HRMS (ESI$^+$) m/z [M + H $^+$]: Calcd. For $C_{19}H_{25}N_2O_3$ 329.1865, found 329.1862.

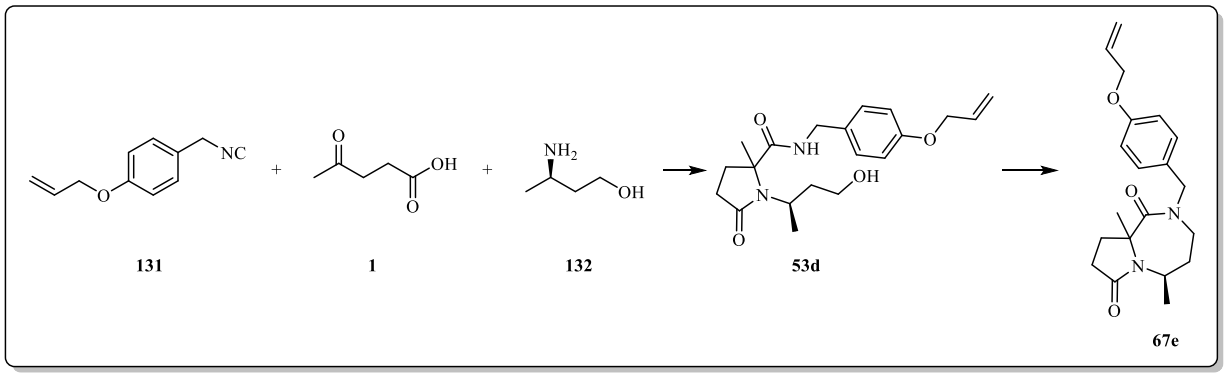
Synthesis of (*R*, *S*)-2-(4-Allyloxyphenyl)-9a-methylhexahydro-1H-pyrrolo[1,2-a][1,4]diazepine-1,7(8H)-dione (67d):



A solution of N-(4-allyloxyphenyl) formamide (417.8 mg, 2.36 mmol) in dry CH_2Cl_2 (3.5 mL) was cooled to 0 °C, and treated with Burgess reagent [(Methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt] (674.8 mg, 2.83 mmol). After stirring for 3h at 0 °C, the crude isocyanide (as CH_2Cl_2) solution was treated with the premixed levulinic acid (210 µL, 2.05 mmol) and propanolamine (150 µL, 1.97 mmol) in dry MeOH mixture (8.1 mL) with 3Å powdered molecular sieves (100 mg). The mixture was stirred at room temperature for 4 days. Then it was diluted with CH_2Cl_2, filtered and the solvents evaporated to dryness. It was taken up in AcOEt/MeOH, 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, and chromatography (AcOEt: DCM 1: 1 + 10% of EtOH), the Ugi product **53c** (318 mg, 50 % from formamide). R_f = 0.3 (AcOEt: DCM 1: 1 + 10% of EtOH). ^{1}H NMR (300 MHz, Chloroform-d) δ 8.40 (bs, NH), 7.51-7.45 (m, Ar, 2H), 6.90-6.84 (m, Ar, 2H), 6.10-5.97 (m, OCH$_2$C*H*, 1H), 5.40 (dq, J= 17.3, 1.61 Hz, CH=C*H*H, 1H), 5.28 (dq, J= 10.5, 1.39 Hz, CH=C*H*H, 1H), 4.51 (dt, J= 5.28, 1.53 Hz, O*CH$_2$*CH, 2H), 3.73-3.65 (m, NC*H$_2$*, 2H), 3.55-3.50 (m, HO*CH$_2$*, 2H), 2.57-2.41 (m, *CH$_2$*C=O, CH*H*CH$_2$C=O, 3H), 2.09-1.65 (m, CH*H*CH$_2$C=O, HOCH$_2$*CH$_2$*, 3H), 1.63 (s, C*CH$_3$*, 3H). ^{13}C NMR (75 MHz, CDCl3, 25°C) δ 177.8, 171.6 (C=O), 133.1, 130.6 (quat.), 121.9 (aromatic CH), 117.7 (OCH$_2$*C*H), 115.0 (aromatic CH), 69.0 (O*CH$_2$*CH), 68.3 (*C*CH$_3$), 60.2 (NC*H$_2$*), 38.8 (HO*CH$_2$*), 33.7 (CH*H*CH$_2$C=O), 30.6 (HOCH$_2$*CH$_2$*), 29.7 (*CH$_2$*C=O), 22.7 (C*CH$_3$*). This intermediate (112.0 mg, 0.339 mmol) was taken up in dry DMF (1 mL) and treated with sulfonyl diimidazole (SDI) (102.4 mg, 517 µmol), and NaH (60 % suspension in mineral oil) (21.8 mg, 545 µmol). The mixture was stirred for overnight at 50°C. Then tris(hydroxymethyl)aminomethane (TRIS) (31.2 mg, 258 µmol) was added, followed by a spatula tip of NaH. After 1h, the mixture was poured into a mixture of $(NH_4)H_2PO_4$ 5 %: NH_4Cl sat. 1:1 and extracted with AcOEt: Et_2O 1: 1. The organic phases were washed with LiCl 5% and Brine.

Chromatography gave pure **67d** as an oil (78.9 mg, 74 %). R_f: 0.37 (AcOEt/MeOH, 99:1). ^{1}H NMR (300 MHz, CDCl3, 25 °C) δ 7.01 (d, J= 8.8 Hz, H meta to OAll, 2H), 6.90 (d, J= 8.8 Hz, H ortho to OAll, 2H), 6.03 (ddt, J= 5.0, 10.5, 17.2 Hz, C*H*=CH_2, 1H), 5.40 (dq, J= 1.5, 17.3 Hz, CH=C*H*H, 1H), 5.28 (dq, J= 1.4, 10.5 Hz, CH=C*H*H, 1H), 4.52 (dt, J= 1.5, J= 5.2Hz, *CH_2*CH=CH_2, 2H), 4.31 (dt, J= 6.4, 13.9 Hz, H-5, 1H), 3.74 and 3.65 (ABXY syst, ^{2}J= 14.8, ^{3}J= 6.6 (ax), 8.7 (bx), 3.0 (ay = by)Hz, H-3, 2H), 3.07 (dt, J= 6.7, J= 13.8 Hz, H-5, 1H), 2.88 (ddd, J= 5.1, 7.7, 12.8 Hz, H-9, 1H), 2.55–2.35 (m, H-8, 2H), 2.18–1.93 (m, H-4, 2H), 1.92 (dt, J= 9.0, J= 12.8 Hz, H-9, 1 H), 1.65 (s, CH_3, 3 H,) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C) δ 174.8, 174.4 (C=O), 157.2, 138.9 (quat,), 133.0 (*C*H=CH_2), 127.3 (C meta to OAll), 117.7 (CH=*C*H_2), 115.4 (C ortho to OAll), 69.0 (*C*CH_3), 67.6 (C-9a), 50.9 (C-3), 36.9 (C-5), 33.7 (C-9) 29.6 (C-8), 27.5 (C-4), 23.1 (CH_3) ppm. HRMS (ESI$^+$) m/z [M + H $^+$]: Calcd. For $C_{18}H_{23}N_2O_3$ 315.1709, found 315.1715.

Synthesis of (5R,9aR) and (5R,9aS)-2-[(4-Allyloxyphenyl)methyl]-5,9a-dimethylhexahydro-1H-pyrrolo[1,2-a][1,4]diazepine-1,7(8H)-diones (67e):



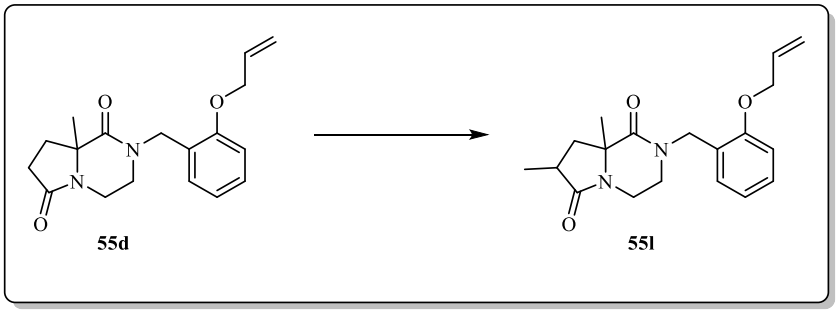
Levulinic acid **1** (324 µL, 3.17 mmol) was dissolved in dry MeOH(17.6 mL), and treated with 3 Å powdered molecular sieves (143 mg), and (*R*)-3-ammino-1-buthanol (248 µL, 2.64 mmol) was added. After 30 min., isocyanide **131** (854.7 mg, 3.43 mmol) was added, and the mixture stirred for 5 days at room temperature. Then it was diluted with CH_2Cl_2, filtered and the solvents evaporated to dryness. It was taken up in AcOEt/MeOH, 95:5 and washed with saturated aqueous $NaHCO_3$. The organic phases gave, upon evaporation, and chromatography (AcOEt: DCM: MeOH 95: 95: 10) the pure Ugi adduct as a brown oil (347.5 mg, 37%). Separation of the two diastereomers was not complete. The diastereomeric ratio, determined by ^{1}H NMR on the crude, was 50:50. **Upper:** R_f = 0.50 (AcOEt: DCM: MeOH 95: 95: 10). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.21-7.17 (m, Ar, 2H), 7.11 (bs, NH), 6.89-6.84 (m, Ar, 2H), 6.04 (ddt, J= 17.2, 10.5, 5.28 Hz, OCH_2C*H*, 1H), 5.40 (dq, J= 17.3, 1.34 Hz, CH=C*H*H, 1H), 5.29 (dq, J= 10.4, 1.11 Hz, CH=C*H*H, 1H), 4.52 (dt, J= 5.27, 1.31 Hz, O*CH_2*CH, 2H), 4.42- 4.30 (m, NH*CH_2*, 2H), 3.70-3.55 (m, NC*H*, HOC*H*H, 2H), 3.50-3.42 (m, HOC*H*H, 1H), 2.77-2.75 (m, OH, 1H), 2.50-2.22 (m, *CH_2*C=O, NCHC*H*H, CH*H*CH_2C=O, 4H), 1.97-1.76 (m, NCHC*H*H, CH*H*CH_2C=O, 2H), 1.59 (s, C*CH_3*, 3H), 1.30 (d, J= 6.80 Hz, CH*CH_3*, 3H). ^{13}C NMR (75 MHz, CDCl3, 25°C) δ 177.1, 173.7 (C=O), 133.1, 130.3 (quat.), 129.3 (aromatic CH), 117.7 (OCH_2*C*H), 114.9 (aromatic CH), 68.8 (O*CH_2*CH), 68.5 (*C*CH_3), 59.7 (HO*CH_2*), 48.4 (N*CH*), 43.3 (NH*CH_2*), 37.6 (NCH*CH_2*), 33.8 (*CH_2*CH_2C=O), 30.2 (*CH_2*C=O), 23.6 (C*CH_3*), 19.1 (CH*CH_3*). **Lower:** R_f = 0.43 (AcOEt: DCM: MeOH 95: 95: 10). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.18-7.13 (m, Ar, 2H), 6.87-6.82 (m, Ar, 2H), 6.40

(bs, NH), 6.02 (ddt, J= 17.2, 10.5, 5.27 Hz, OCH_2CH, 1H), 5.39 (dq, J= 17.3, 1.55 Hz, CH=C*H*H, 1H), 5.27 (dq, J= 10.5, 1.32 Hz, CH=C*H*H, 1H), 4.50 (dt, J= 5.26, 1.46 Hz, OCH_2CH, 2H), 4.35 (d, J= 5.60 Hz, $NHCH_2$, 2H), 3.64-3.92 (m, NC*H*, $HOCH_2$, 3H), 2.49-2.19 (m, CH_2C=O, NCHC*H*H, 3H), 2.08-1.84 (m, NCHC*H*H, $HOCH_2$, 3H), 1.54 (s, CCH_3, 3H), 1.34 (d, J= 6.87 Hz, $CHCH_3$, 3H). ^{13}C NMR (75 MHz, CDCl3, 25°C) δ 176.2, 177.3 (C=O), 133.1, 129.9 (quat.), 129.2 (aromatic CH), 117.7 (OCH_2CH), 115.0 (aromatic CH), 68.8 (OCH_2CH), 68.5 (CCH_3), 59.5 ($HOCH_2$), 47.7 (N*CH*), 43.5 ($NHCH_2$), 37.0 ($NCHCH_2$), 33.2 (CH_2CH_2C=O), 30.3 (CH_2C=O), 22.9 (CCH_3), 17.7 ($CHCH_3$). The two diastereomers were cyclized independently. **Upper** and **lower** refers to the TLC behavior of intermediate Ugi adducts, since, after cyclization, they had the same R_f.

Upper (Method A): The Ugi adduct was taken up in dry DMF (1 mL) and treated with sulfonyl diimidazole (SDI) (132.5 mg, 668 µmol), and NaH (60 % suspension in mineral oil) (28.8 mg, 720 µmol). The mixture was stirred for overnight at 50°C. Then tris(hydroxymethyl)aminomethane (TRIS) (33.2 mg, 274 µmol) was added, followed by a spatula tip of NaH. After 1h, the mixture was poured into a mixture of $(NH_4)H_2PO_4$ 5 %: NH_4Cl sat. 1:1 and extracted with AcOEt: Et_2O 1: 1. The organic phases were washed with LiCl 5% and Brine. Chromatography (AcOEt) gave pure **67e** as an oil (68.2 mg, 45 %). $[\alpha]_D$ = –12.6 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz $CDCl_3$, 25 °C) δ 7.17 (d, J = 8.7 Hz, H meta to OAll, 2H,), 6.87 (d, J = 8.7 Hz, H ortho to OAll, 2H), 6.05 (ddt, J = 10.5, 17.2, 5.3 Hz, C*H*=CH_2, 1H), 5.41 (dq, J = 1.6, 17.2 Hz, CH=C*H*H, 1 H), 5.29 (dq, J= 1.4, 10.5 Hz, CH=C*H*H, 1 H), 4.56 and 4.47 (AB syst, J= 14.3 Hz, ArCH_2, 2 H), 4.52 (dt, J = 1.5, 5.4 Hz, CH_2CH= CH_2, 2H), 3.44 (ddd, J= 4.4, 12.4, 15.1 Hz, H-3, 1H), 3.26 (dquint, J= 6.7, 11.4 Hz, H-5, 1H), 3.14 (ddd, J= 1.2, 5.1, 5.1 Hz, H-3, 1H), 2.68–2.51 (m, H-9, 1H), 2.36–2.22 (m, 2 H, H-8); 2.19–2.07 (m, H-9, 1H), 1.91 (1 H, dddd, J= 1.5, 4.5, 11.7, J= 13.2 Hz, 1 H, H-4); 1.67–1.53 (m, H-4, 1H), 1.60 (d, J= 6.9 Hz, CH_3CH, 3H), 1.59 (s, CH_3C, 3H) ppm. ^{13}C NMR (75 MHz CDCl3, 25 °C) δ 174.9, 173.7 (C=O), 158.1, 129.7 (quat,), 133.1 (*C*H=CH_2), 129.3 (C meta to OAll), 117.7 (CH=*C*H_2), 114.9 (C ortho to OAll), 69.3(*C*CH_3), 68.8 (C-9a), 52.2 (N-*C*H_2Ar), 48.5 (C-5), 45.3 (C-3), 31.7 (C-9) 31.6 (C-4), 30.6 (C-8), 24.4 (C-*C*H_3), 17.4 ($CHCH_3$) ppm. HRMS (ESI^+) m/z [M + H $^+$]: Calcd. For $C_{20}H_{27}N_2O_3$ 342.2022, found 343.2019.

Lower: It was prepared in 53% yield from the lower diastereomer of Ugi adduct following method A. $[\alpha]_D$ = +136.2 (c = 1, $CHCl_3$). ^{1}H NMR (300 MHz $CDCl_3$, 25 °C) δ 7.13 (d, J= 8.6 Hz, H meta to OAll, 2H), 6.86 (d, J= 8.6 Hz, 2H, H ortho to OAll) 6.05 (ddt, J= 10.5, 17.2, 5.3 Hz, C*H*=CH_2, 1 H), 5.41 (dq, J= 1.6, 17.3 Hz, CH=C*H*H, 1 H), 5.29 (dq, J= 1.5,10.5 Hz, CH=C*H*H, 1 H), 4.62 and 4.41 (AB syst, J= 14.4 Hz, ArCH_2, 2H), 4.52 (dt, J= 1.5, 5.3 Hz, CH_2CH=CH_2, 2 H), 4.50–4.35 (m, H-5, 1H), 3.30–3.12 (m, H-3, 2H), 2.79 (ddd, J= 8.2, 4.7, 12.9 Hz, H-9, 1H), 2.45–2.25 (m, H-8, 2H); 2.16–1.72 (m, H-9, H-4, 3H), 1.71 (s, C*H*$_3$C, 3H), 1.26 (d, J= 6.9 Hz, CH_3CH, 3H) ppm. ^{13}C NMR (75 MHz CDCl3, 25 °C) δ 175.6, 174.8 (C=O), 158.1, 129.3 (quat,), 133.2 (CH=CH_2), 129.2 (C meta to OAll), 117.7 (CH=CH_2), 114.9 (C ortho to OAll), 68.8 (*C*CH_3), 68.6 (C-9a), 53.0 (N-CH_2Ar), 47.6 (C-5), 46.6 (C-3), 35.6 (C-9) 34.0 (C-4), 29.4 (C-8), 28.0 (C-*C*H_3), 20.5 ($CHCH_3$) ppm. HRMS (ESI^+) m/z [M + H $^+$]: Calcd. For $C_{20}H_{27}N_2O_3$ 342.2022, found 343.2017.

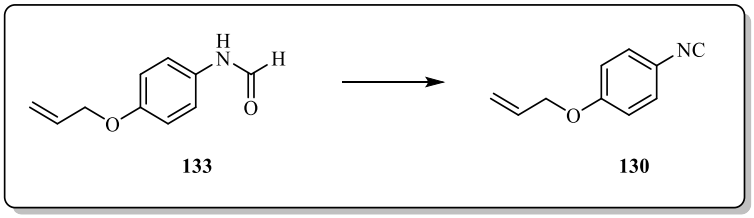
Synthesis of 2-(2-Allyloxybenzyl)-7,8a-dimethyltetrahydropyrrolo[1,2-a]pyrazine-1,6(2H,7H)-dione (55l):



A 0.4 M solution of LDA was prepared at –20 °C by adding nBuLi (1.6 M in hexanes, 5.0 mL, 8.0 mmol) to a solution of diisopropylamine (1.24 mL, 8.8 mmol) in dry THF (12.3 mL) containing few crystals of 2,2′-bipyridyl and stirring for 20 min. Part of this deep red solution (3.10 mL corresponding to 1.24 mmol) was transferred via syringe into another flask, again cooled to –20 °C. To this flask, a solution of compound **55d** (257 mg, 818 μmol) dissolved in dry THF (2 mL + 0.5 mL + 0.5 mL for washing) was added. After 20 min (the solution lose its deep red color) the flask was cooled to –78°C, and methyl iodide(77μL,1.24mmol) was added. The temperature was allowed to rise slowly to –30 °C during 3 h. Then the reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. Evaporation and chromatography (CH_2Cl_2/AcOEt, 1:1 + 1.5 % MeOH) gave pure **55l** as a foam (180 mg, 67 %). Also 40 mg of starting **55d** were recovered. Thus, the yield from unrecovered substrate was 79 %. R_f = 0.56 (CH_2Cl_2/ AcOEt, 1:1 + 5 % MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) (note: two diastereomers, in a 91:9 ratio are detected). The diastereomeric ratio was calculated by integration of the CH_3CH signals (minor diast. resonates at 1.27. Here, only the signals of major diastereomer are reported) δ 7.30–7.15 (m, H meta to Oallyl, 2H), 6.93 (dt, J= 0.9, 7.5 Hz, H para to Oallyl, 1H), 6.87 (d, J= 8.2 Hz, H ortho to Oallyl, 1H), 6.04 (ddt, J= 10.4, 17.2, 5.1 Hz, C*H*=CH_2, 1 H), 5.40 (dq, J= 1.6, J= 17.3 Hz, CH=C*H*H, 1H), 5.28 (dq, J= 1.4, 10.5 Hz, CH=C*H*H, 1 H), 4.73 and 4.60 (AB syst, J= 14.7 Hz, *CH_2*Ar, 2H), 4.55 (dt, J= 1.5, J= 5.1 Hz, *CH_2*CH=, 2H], 4.09 (ddd, J= 1.4, 5.0, 13.4 Hz, H-4, 1H), 3.38 (dt, = 5.0, 11.7, 1.7 Hz, H-3, 1H), 3.28–3.08 (m, H-3 and H-4, 2H), 2.69–2.52 (m, H-7, 1H), 2.44 (dd, J= 8.1, J= 12.9 Hz, H-8, 1H), 1.82 (dd, J= 11.0, 12.9 Hz, H-8, 1H), 1.51 (s, CH_3, 3H), 1.19 (d, J= 7.0 Hz, *CH_3*CH, 3H) ppm. ^{13}C NMR (75 MHz, CDCl3, 25 °C) δ 174.7, 171.5 (C=O), 156.6, 124.6 (quat,), 133.0 (*C*H=CH_2), 129.7, 128.9 (C meta to Oallyl), 121.0 (C para to Oallyl), 117.5 (CH=*C*H_2), 111.6 (C ortho to Oallyl), 68.8 (O*C*H_2), 60.5 (C-8a), 46.2 (C-3); 44.8 (*C*H_2Ar), 40.1 (C-8), 35.1 (C-7), 33.8 (C-4), 22.7 (*C*H_3C), 15.3 (*C*H_3CH) ppm. HRMS (ESI$^+$) m/z [M + H $^+$]: Calcd. For $C_{19}H_{25}N_2O_3$ 329.1865, found 329.1858.

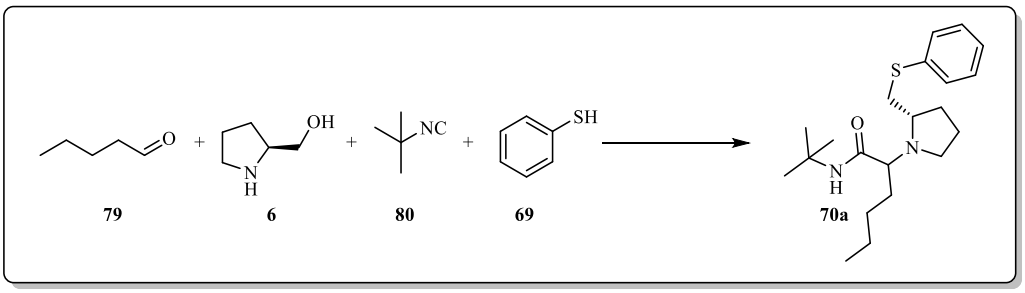
3.3 Synthesis of tertiary amines

Synthesis of 1-(allyloxy)-4-isocyanobenzene (130)



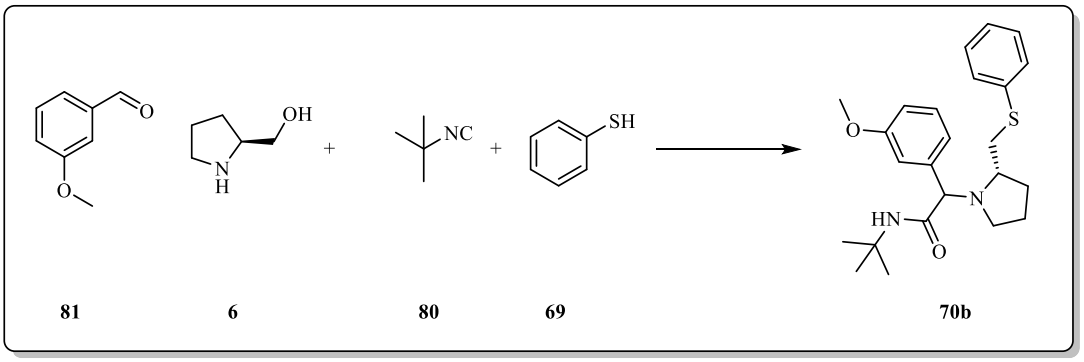
N-(4-(allyloxy)phenyl)formamide **133** (452.0 mg, 2.55 mmol) and Et_3N (1.6 mL, 11.5 mmol) were dissolved in dry DCM (25 mL) and the solution was cooled at -30°C. $POCl_3$ (0.350 mL, 3.75 mmol) was dropped into the solution and the reaction mixture was stirred for 1.5 h. It was diluted with Et_2O, washed with $NaHCO_3$ and the solvent was removed under reduced pressure. The crude product was purified through chromatographic column and the desired product was obtained as a green oil (192.0 mg, 48%). ^{1}H-NMR was in accordance with data reported in literature.[48]

Synthesis of N-(tert-butyl)-2-(2-((phenylthio)methyl)pyrrolidin-1-yl)hexanamide (70a)



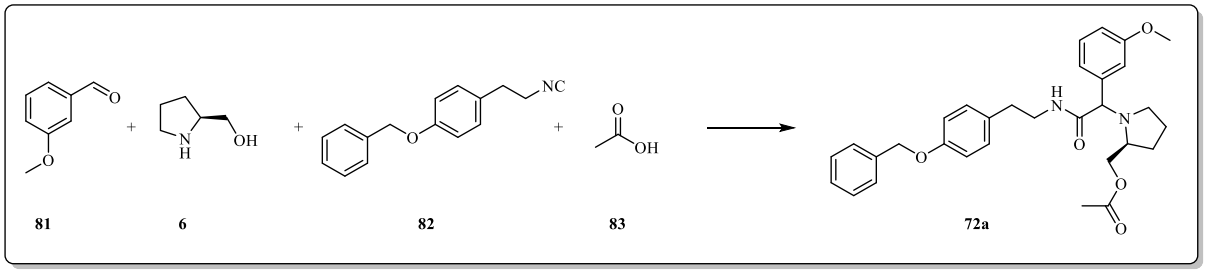
Pentanal **79** (130 µL, 2.06 mmol), L-prolinol **6** (200 µL, 2.06 mmol) were added in dry MeOH (2 mL) and the reaction was stirred for 2h at room temperature. Then ^{t}Butyl-isocyanide **80** (280 µL, 2.47 mmol) and thiophenol **69** (250 µL, 2.44 mmol) were added and the reaction mixture was stirred at 100 °C overnight. The solvent was removed under reduced pressure and the crude product was purified through chromatographic column to afford the desired product as a yellow solid (363.0 mg, 1.00 mmol, 50%). R_f = 0.38 (PE: AcOEt 5:1 and 1% EtOH). $[\alpha]_D$ = -44.1 (c = 0.9, $CHCl_3$). m.p. = 44.3-46.3 °C. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.35-7.23 (m, Ar, 4H), 7.19-7.13 (m, Ar, 1H), 6.24 (s, NH, 1H), 3.20-3.12 (m, N*CH*CH_2, 1H), 3.08-2.94 (m, S*CH*$_2$, N*CH*$_2$, CO*CH*, 3H), 2.86-2.71 (m, S*CH*$_2$, N*CH*$_2$, 2H), 2.20-1.90 (m, NCH*CH*$_2$, 1H), 1.83-1.69 (m, NCH*CH*$_2$, NCH_2*CH*$_2$, 3H), 1.68-1.50 (m, COCH*CH*$_2$, 2H), 1.34-1.24 (m, $COCHCH_2$*CH*$_2$$CH_2$, $COCHCH_2CH_2$*CH*$_2$, ^{t}Butyl, 13H), 0.89-0.84 (m, CH_3, 3H). ^{13}C NMR (75 MHz, Chloroform-d) δ 172.7 (C=O), 136.7 (quat.) 129.1, 128.9, 125.9 (aromatic CH), 67.0 (CO*CH*), 58.3 (N*CH*CH_2), 51.9 (N*CH*$_2$), 39.8 (S*CH*$_2$), 31.0 ($COCH$*CH*$_2$$CH_2$), 30.9 (NCH*CH*$_2$), 28.8 ($COCHCH_2$*CH*$_2$$CH_2$), 28.7 (^{t}Butyl), 23.3 (NCH_2*CH*$_2$), 22.8 ($COCHCH_2CH_2$*CH*$_2$), 14.0 (CH_3). I.R. (ATR): ν_{max}: 3269, 3074, 2965, 2924, 2869, 2825, 1649, 1551, 1455, 1390, 1359, 1303, 1263, 1229, 1136, 1096, 1024, 908, 742, 690, 636.

Synthesis of N-(tert-butyl)-2-(3-methoxyphenyl)-2-(2-((phenylthio)methyl)pyrrolidin-1-yl)acetamide (70b)



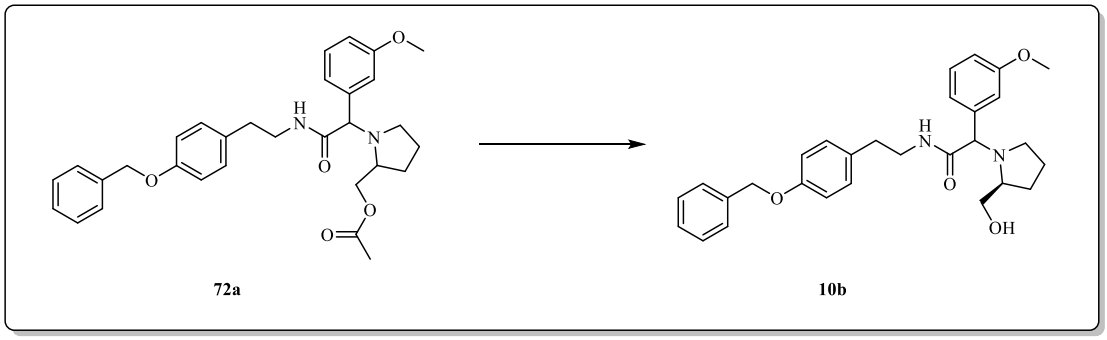
Molecular sieves (206 mg) were added to a solution of *m*-methoxy-benzaldehyde **81** (0.156 mL, 1.28 mmol) and L-prolinol **6** (0.130 mL, 1.34 mmol) in dry DCM (13 mL). The reaction mixture was stirred at r.t. overnight. It was filtered and the solvent was removed to obtain the crude product (293.8 mg) as a red oil. This crude product (236.3 mg, theoretical 1.07 mmol) was then dissolved in dry MeOH (1.1 mL) and ^{t}Butyl isocyanide **80** and thiophenol **69** were then added. The reaction mixture was stirred at 100 °C overnight. After filtration, it was diluted in AcOEt, washed with a mixture of Na_2CO_3: Brine 1:1 and the solvent was removed under reduced pressure. The crude product was purified through chromatographic column (PE:AcOEt 6:1 up to 4:1 and 1% of EtOH) to obtain the desired product (yellow oil, 285.2 mg, 63%) as a mixture of diastereoisomers. The d.r. was = 90:10 by HPLC of the obtained fractions. Conditions: column Gemini C6-Phenyl 150x3 mm, 3µ. Flow: 0.34 ml/min. Temp = 30°C. Eluent: H_2O + 0.1% HCOOH: MeOH + 0.1% HCOOH 90:10 up to 20 min. Then MeOH + 0.1% HCOOH 100%. R_f = 0.30 (PE: AcOEt 3:1). $[\alpha]_D$ = -19.2 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.24-7.05 (m, Ar diast. A+B, 5H), 6.98-6.93 (m, Ar diast. A+B, 3H), 6.86-6.83 (m, Ar diast. A+B, 1H), 4.22 (s, CO*CH* diast. B, 1H), 3.93 (s, CO*CH* diast. A, 1H), 3.77 (s, O*CH*$_3$ diast. B, 3H), 3.76 (s, O*CH*$_3$ diast. A, 3H), 3.16-3.02 (m, N*CH*CH_2, SC*H*H diast. A+B, 2H), 2.81 (dd, N*CH*H diast. A+B, J= 12.7, 4.03 Hz, 1H), 2.69-2.61 (m, SC*H*H diast. A+B, 1H), 2.50 (dd, SC*H*H diast. A+B, J= 12.7, 8.56 Hz, 1H), 1.98-1.72 (m, NCH*CH*$_2$, NCH$_2$*CH*$_2$ diast. A+B, 4H), 1.38 (s, ^{t}Butyl diast. A, 9H), 1.3 (s, ^{t}Butyl diast. B, 9H). ^{13}C NMR (75 MHz, Chloroform-d) δ 170.9 (C=O diast. A), 159.6, 139.1, 136.7 (quat. diast. A), 129.5, 129.0, 128.7, 128.2, 125.4, 121.4, 114.4, 114.1 (aromatic CH diast. A), 75.1 (CO*CH* diast. A), 69.9 (CO*CH* diast. B), 59.0 (N*CH* diast. A), 55.1 (*CH*$_3$ diast. A), 54.8 (S*CH*$_2$ diast. A), 39.5 (N*CH*$_2$ diast. A), 30.4 (NCH*CH*$_2$ diast. A), 28.8 (^{t}Butyl diast. A), 23.6 (NCHCH$_2$*CH*$_2$ diast. A). I.R. (ATR): ν_{max}: 3323, 3058, 2963, 3871, 2835, 1662, 1584, 1511, 1481, 1452, 1437, 1391, 1363, 1317, 1259, 1225, 1153, 1110, 1088, 1044, 737, 690.

Synthesis of (1-(2-((4-(benzyloxy)phenethyl)amino)-1-(3-methoxyphenyl)-2-oxoethyl)pyrrolidin-2-yl)methyl acetate (72a)



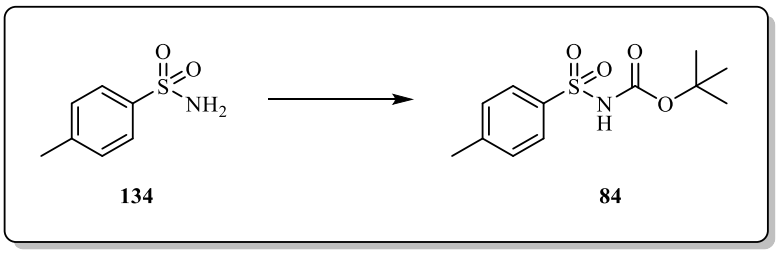
Molecular sieves (159 mg) were added to a solution of *m*-methoxy-benzaldehyde **81** (0.120 mL, 0.987 mmol) and L-prolinol **6** (0.100 mL, 1.03 mmol) in dry DCM (10 mL). The reaction mixture was stirred at r.t. overnight. It was filtered and the solvent was removed to obtain the crude product (226 mg, theoretical 0.987 mmol) as a red oil. It was dissolved in dry MeCN (2.5 mL) and 1-(benzyloxy)-4-(2-isocyanoethyl)benzene **77** (281.0 mg, 1.2 mmol), acetic acid **83** (68.0 µL, 1.21 mmol), *p*-toluensulphonic acid (19.6 mg, 0.103 mmol) and molecular sieves (30 mg) were added. The reaction mixture was stirred under reflux overnight. After filtration, it was diluted in AcOEt, washed with $NaHCO_3$ and Brine and the solvent was removed under reduced pressure. The crude product was purified through chromatographic column (PE: AcOEt 2:1 and 1% of EtOH) to obtain the desired product (yellow oil, 281.4 mg, 55%) as a mixture of diastereoisomers (d.r. = 91:9, determined through ^{1}H-NMR of the obtained fractions). The d.r. was = 87:13 by HPLC of the crude product. Conditions: column Gemini C6-Phenyl 150x3 mm, 3µ. Flow: 0.34 ml/min. Temp = 30°C. Eluent: H_2O + 0.1% HCOOH: MeOH + 0.1% HCOOH 70:30 up to 30 min. Then MeOH + 0.1% HCOOH 100%. R_f = 0.20 (PE: AcOEt 2:1). $[\alpha]_D$ = +24.7 (c = 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.46-7.30 (m, Ar diast. A+B, 5H), 7.23-7.18 (m, Ar diast. A+B, 1H), 7.11-7.08 (m, Ar diast. A+B, 2H), 7.00-6.97 (t, J= 5.57 Hz, NH, 1H), 6.92-6.80 (m, Ar diast. A+B, 5H), 5.05 (s, Ph*CH*$_2$O diast. A, 2H), 4.41 (s, CO*CH* diast. B), 1H), 4.08 (s, CO*CH* diast. A, 1H), 3.78 (s, O*CH*$_3$ diast. B, 3H), 3.77 (s, O*CH*$_3$ diast. A, 3H), 3.69 (m, CH*CH*$_2$O diast. A+B, 2H), 3.57-3.50 (m, NH*CH*$_2$ diast. A+B, 2H), 3.03-2.97 (m, N*CH* diast. A+B, 1H), 2.91-2.83 (m, NCH*H* diast. A+B, 1H), 2.79 (t, J= 6.92 Hz, NHCH$_2$*CH*$_2$ diast. A+B, 2H), 2.63-2.55 (m, NCH*H* diast. A+B, 1H), 1.98 (s, CO*CH*$_3$ diast. A+B, 3H), 1.88-1.50 (m, NCH*CH*$_2$, NCH$_2$*CH*$_2$ diast. A+B, 4H). ^{13}C NMR (75 MHz, Chloroform-d) δ 171.5, 170.9 (C=O), 159.6, 157.5, 139.0, 137.0, 131.1 (quat.), 129.7, 129.5, 128.6, 127.9, 127.4, 121.1, 114.9, 114.8, 113.5 (aromatic CH), 73.8 (CO*CH*), 70.0 (Ph*CH*$_2$O), 66.6 (CH*CH*$_2$O), 58.4 (N*CH*), 55.2 (O*CH*$_3$), 53.7 (N*CH*), 40.3 (NH*CH*$_2$), 34.7 (NHCH$_2$*CH*$_2$), 28.0 (NCH*CH*$_2$), 23.5 (NCHCH$_2$*CH*$_2$), 20.9 (CO*CH*$_3$). I.R. (ATR): ν_{max}: 3314, 2943, 2873, 2836, 1733, 1659, 1607, 1509, 1453, 1366, 1230, 1175, 1035, 745, 694.

Synthesis of N-(4-(benzyloxy)phenethyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(3-methoxyphenyl)acetamide (10b)



(1-(2-((4-(benzyloxy)phenethyl)amino)-1-(3-methoxyphenyl)-2-oxoethyl)pyrrolidin-2-yl)methyl acetate **72a** (168.7 mg, 0.326 mmol) was dissolved in MeOH (0.63 mL) and a solution of KOH in MeOH 1M (0.656 mL, 0.656 mmol) was added. The reaction mixture was stirred for 40 min. It was diluted with AcOEt and washed with a mixture of NH_4Cl sat.: $NaHCO_3$ sat.: NaCl sat. 10:5:40. After checking pH = 8 the solvent was removed under reduced pressure. The crude product was purified through chromatographic column (AcOEt: DCM 1:1 and 5% of MeOH) to obtain the desired product (yellow oil, 118 mg, 76%) as a mixture of diastereoisomers (d.r. = 89:11, determined through ^{1}H-NMR of the obtained fractions). R_f = 0.3 (AcOEt: DCM 1:1 and 5% of MeOH). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.45-7.29 (m, Ar diast. A+B, 5H), 7.26-7.18 (m, Ar diast. A+B, 1H), 7.08-7.01 (m, Ar diast. A+B, 2H), 6.92-6.80 (m, Ar diast. A+B, 5H), 6.69 (t, J= 5.55 Hz, NH, 1H), 5.04 (s, Ph*CH*$_2$O diast. A+B, 2H), 4.22 (s, CO*CH* diast. B, 1H), 4.11 (s, CO*CH* diast. A, 1H), 3.78 (s, O*CH*$_3$ diast. B, 3H), 3.77 (s, O*CH*$_3$ diast. A, 3H), 3.52 (q, J= 6.74 Hz, NH*CH*$_2$ diast. A+B, 2H), 3.15 and 3.04 (ABX syst, J= 10.8 (ab), 4.75 (ax), 4.55 (bx) Hz, *CH*$_2$OH diast. A+B, 2H), 2.92 (m, N*CH* diast. A+B, NC*H*H, 2H), 2.76 (m, NHCH$_2$*CH*$_2$ diast. A+B, 2H), 2.70-2.61 (m, NC*H*H diast. A+B, 1H), 1.86-1.52 (m, NCH*CH*$_2$, NCH$_2$*CH*$_2$ diast. A+B, 4H). ^{13}C NMR (75 MHz, Chloroform-d) δ 170.2 (C=O), 159.6, 157.5, 138.9, 137.0 (quat.), 131.0, 129.7, 129.6, 128.6, 127.9, 127.4, 121.0, 115.0, 114.7, 113.6 (aromatic CH), 73.1 (CO*CH* diast. A), 70.7 (CO*CH* diast. B), 70.0 (Ph*CH*$_2$O), 64.1 (*CH*$_2$OH), 61.7 (CO*CH*), 55.2 (O*CH*$_3$), 53.6 (N*CH*$_2$), 40.4 (NH*CH*$_2$), 34.6 (NHCH$_2$*CH*$_2$), 28.0 (NCH*CH*$_2$), 23.7 (NCHCH$_2$*CH*$_2$).

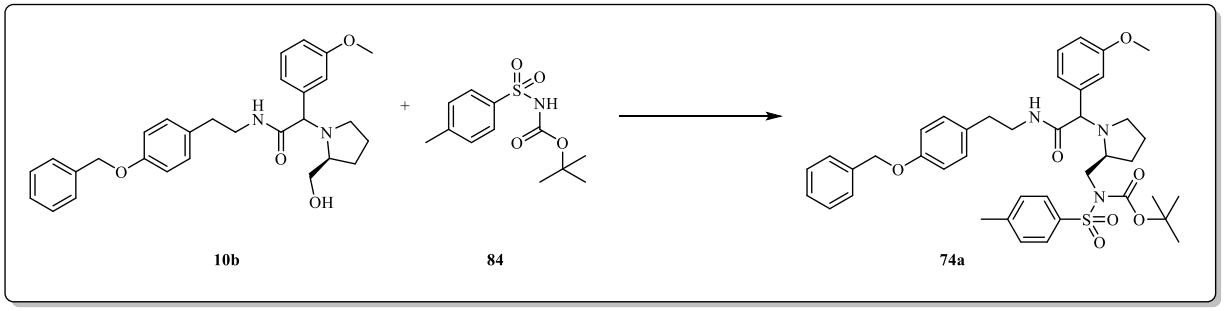
Synthesis of Boc-*p*-toluensulphonamide (84)



p-Toluensulfonamide **134** (501.0 mg, 2.92 mmol) was dissolved in dry DCM (6 mL). $(Boc)_2O$ (700.0 mg, 3.21 mmol), DMAP (70.0 mg, 0.58 mmol) and Et_3N (0.49 mL, 3.50 mmol) were added and the reaction mixture was stirred at room temperature overnight. It was cooled at 0°C and HCl 1M (5 mL) was added. The mixture was extracted with AcOEt and the organic phases were washed with $NaHCO_3$, brine and the solvent was removed under reduced

pressure. The crude product was purified through chromatographic column (PE:AcOEt: 3:1) to obtain the desired product as a white solid (379.0 mg, 49%).

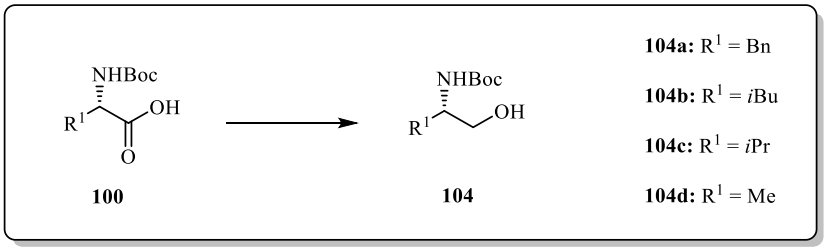
Synthesis of tert-butyl-((1-(2-((4-(benzyloxy)phenethyl)amino)-1-(3-methoxyphenyl)-2-oxoethyl)pyrrolidin-2-yl)methyl)(tosyl)carbamate (74a)



N-(4-(benzyloxy)phenethyl)-2-(2-(hydroxymethyl)pyrrolidin-1-yl)-2-(3-methoxyphenyl)acetamide **10b** (71.4 mg, 0.150 mmol) was dissolved in dry DCM (1.5 mL). ^{t}Butyl tosylcarbamate **84** (48.7 mg, 0.179 mmol) was added and the solution was cooled to 0°C. TBAD (51.9 mg, 0.225 mmol) and Ph_3P (59.6 mg, 0.227 mmol) were added and the reaction mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified though chromatographic column (PE: AcOEt 2:1 and 1% of EtOH). to obtain the desired product (78.9 mg, 72%) as a colorless oil. The two diasteroisomers were not completely separated. Both the major (diast. A) and the minor (diast. B) were obtained as a mixture with the opposite diastereoisomer (d.r. = 97:3, determined through ^{1}H-NMR of the obtained fractions). R_f (A) = 0.25 (PE: AcOEt 2:1 and 1% of EtOH), R_f (B) = 0.30 (PE: AcOEt 2:1 and 1% of EtOH). Diast. A: $[\alpha]_D$ = +30.2 (c = 0.9, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.92 (t, J= 5.87 Hz, NH, 1H), 7.76-7.70 (m, Ar diast. A+B, 2H), 7.43-7.27 (m, Ar diast. A+B, 7H), 7.20-7.15 (m, Ar diast. A+B, 3H), 7.04-7.02 (m, Ar diast. A+B, 1H), 7.98-6.96 (m, Ar diast. A+B, 1H), 6.91-6.87 (m, Ar diast. A+B, 2H), 6.80-6.75 (m, Ar diast. A+B, 1H), 5.05 (s, Ph*CH*$_2$O diast. B, 2H), 5.01 (s, Ph*CH*$_2$O diast. A, 2H), 4.02 (s, CO*CH* diast. A, 1H), 3.90 (s, CO*CH* diast. B, 1H), 3.80 (s, O*CH*$_3$ diast. A, 3H), 3.77 (s, O*CH*$_3$ diast. B, 3H), 3.75-3.67 (m, NCHC*H*HN diast. A+B, 1H), 3.60-3.52 (m, NH*CH*$_2$ diast. A+B, 2H), 3.42 (dd, J= 14.4, 4.59 Hz, NCHC*H*HN diast. A+B, 1H), 3.26-3.12 (m, NC*H*H, N*CH* diast. A+B, 2H), 2.86 (t, J= 7.57 Hz, NHCH$_2$*CH*$_2$ diast. A+B, 2H), 2.79-2.64 (m, NC*H*H diast. A+B, 1H), 2.43 (s, CH_3 diast. A+B, 3H), 1.96-1.71 (m, NCH*CH*$_2$, NCH$_2$*CH*H diast. A+B, 3H), 1.60-1.41 (m, NCH$_2$*CH*H diast. A+B, 1H), 1.31 (s, ^{t}Butyl diast. B, 9H) 1.15 (s, ^{t}Butyl diast. A, 9H). ^{13}C NMR (75 MHz, Chloroform-d) δ 170.5 (C=O), 159.8, 157.2, 150.5, 143.9, 139.2, 137.8, 137.2 (quat.), 131.6, 129.8, 129.6, 129.2, 128.5, 127.8, 127.6, 127.4, 121.4, 114.7, 114.5, 113.4 (aromatic CH), 73.7 (CO*CH*), 70.0 (Ph*CH*$_2$O), 59.4 (N*CH*), 55.1 (O*CH*$_3$), 51.5 (N*CH*$_2$CH$_2$), 49.8 (N*CH*$_2$CHN), 40.6 (NH*CH*$_2$), 34.8 (NHCH$_2$*CH*$_2$), 27.8 (^{t}Butyl diast. B), 27.7 (^{t}Butyl diast. A), 26.6 (NCH*CH*$_2$), 22.2 (NCHCH$_2$*CH*$_2$), 21.5 (*CH*$_3$). I.R. (ATR): ν_{max} (diast. A): 3351, 2972, 2933, 2873, 1752, 1665, 1598, 1509, 1454, 1346, 1241, 1153, 1087, 1041, 947, 809, 749, 695, 669.

3.4 Synthesis of secondary amines

General procedure for the synthesis of Boc-protected amino alcohols 104a-d from the corresponding Boc-α-amino acids.



Boc-amino acid was dissolved in dry THF (1 mL/mmol). This solution was cooled at -10 °C, and isobutyl chloroformate (1.2 eq.) and N,Ndiisopropylethylamine (1.5 eq.) were added in this order. The mixture was stirred at – 10 °C for 1h. Then it was filtered and the filtrate was cooled at -10 °C and treated with $NaBH_4$ (1.5 eq.) and H_2O (3 mL/mmol of $NaBH_4$), in this sequence. After stirring at -10 °C for 30 min and at rt for 1h, the mixture was diluted with AcOEt and with saturated aqueous NH_4Cl and 5% aqueous $(NH_4)H_2PO_4)NH_4$ (resulting pH = 5). After phase separation, the organic phases were washed with brine, and evaporated to dryness. Chromatography afforded the pure products.

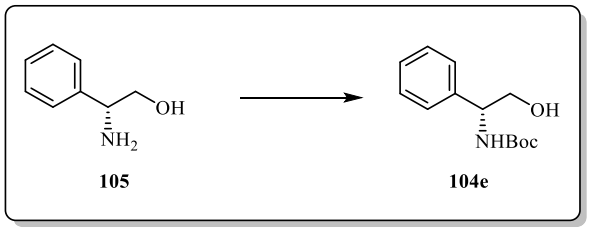
104a. Chromatography: PE/AcOEt/CH_2Cl_2 2:1:2. Yield: 88%. Only (S)-compound was prepared and used. This compound is known.[95]

104b. Chromatography: PE/AcOEt/CH_2Cl_2 1:1:1. Yield: 87%. Only (S)-compound was prepared and used. This compound is known.[96]

104c. Chromatography: PE/AcOEt 3:1. Yield: 87%. Only (S)-compound was prepared and used. This compound is known.[96]

Using the same procedure, both (R)- and (S)-**104d** were prepared. Chromatography with PE: AcOEt: CH_2Cl_2 2:1:1 afforded the products in 67% and 58% yield respectively from the corresponding amino alcohols. They are both known.[96]

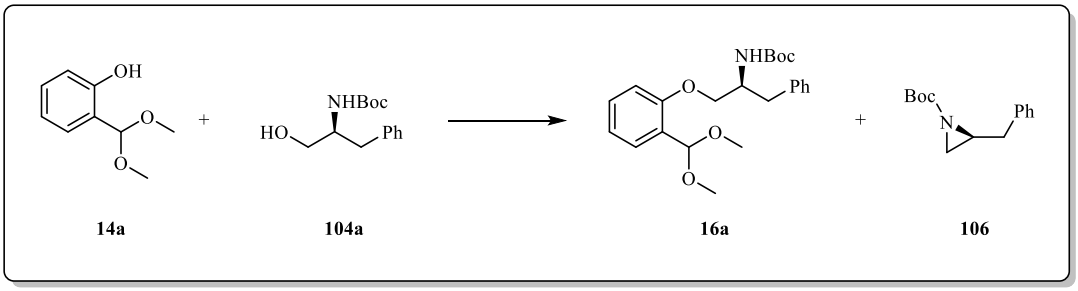
Synthesis of tert-butyl (*R*)-(2-hydroxy-1-phenylethyl)carbamate (104e)



R-(-)-2-phenyl glycinol **105** (1.010 g, 7.36 mmol) was dissolved in dry CH_2Cl_2 (12.3 mL). Et_3N (1.13 mL, 8.11 mmol) and $(Boc)_2O$ (1.771 g, 8.11 mmol) were added at this solution. The mixture was stirred overnight at room temperature, then it was diluted with CH_2Cl_2 and with HCl 1M. After phase separation, the organic phases were washed with saturated aqueous $NaHCO_3$, and evaporated to dryness. The crude product was purified by chromatography using PE: AcOEt: CH_2Cl_2 2:1:1. The product (1.500 g, 6.32 mmol) was obtained as a white solid with a yield of 86,0%. This product is known.[97]

Optimization of the Mitsunobu reaction to give 16a

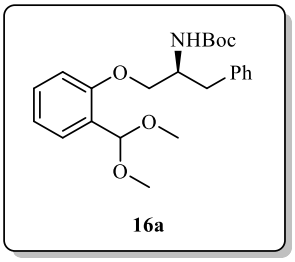
The reaction was first optimized using stoichiometric quantities of the two reagents. Thus, all the following reactions were carried out in THF at 0°C for 3 h and then at rt overnight, using 1 eq. each of **14a** and **104a** and 1.5 eq. of PPh3 and of azodicarboxylate. A main side-product was detected, corresponding to Boc-aziridine **106**.



14a **104a** **16a** **106**

Then, also taking into account the fact that the Boc-amino alcohol is more precious than the salicyladehyde, we decided to use a slight excess (1.2 equiv.) of salicylaldehyde. Finally, we noticed that a slight better yield was achieved by adding PPh_3 and azodicarboxylate in three portions.

Typical procedure for the Mitsunobu reaction: synthesis of (S)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-3-phenylpropan-2-yl)carbamate (16a).

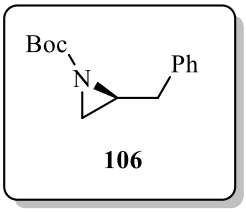


16a

A solution of salicylaldehyde (0.770 mL, 7.38 mmol) in dry MeOH (8.1 mL) was treated with trimethyl orthoformate (3.50 mL, 32.0 mmol) and Amberlyst 15 (100 mg). The resulting mixture was stirred at room temperature for 20 h, then diluted with CH_2Cl_2 and filtered. The filtrate was treated with solid $NaHCO_3$ (25 mg) and filtered again. The filtrate was evaporated, and the residue was taken up in CH_2Cl_2/toluene, and again evaporated to azeothropically remove all methanol. The crude acetal **14a** was obtained as a yellow oil (1.380 g). This acetal (301.7 mg, theoretical 1.61 mmol) was dissolved in dry THF (2.60 mL), cooled to 0°C, and treated sequentially with Boc-amino alcohol 7a (330.5 mg, 1.31 mmol), PPh_3 (171.8 mg, 0.655 mmol) and 1,1'-(Azodicarbonyl)dipiperidine (ADDP) (165.5 mg, 0.656 mmol). After stirring at 0°C for 60 min, further PPh3 (171,8 mg, 0,655 mmol) and ADDP (165,5 mg, 0,656 mmol) were added. Finally, after 60 minutes, an identical amount of both reagents was added. The mixture was further stirred overnight at rt and evaporated to dryness. The crude was taken up in Et_2O and washed with NaOH 1M, to remove excess of **14a**. The organic phase was washed with aqueous saturated NH_4Cl, evaporated and purified by chromatography (PE: AcOEt 11:1) to give pure **16a** as an oil (411.4 mg, 78% from **104a**). R_f = 0.20 (PE / AcOEt 10:1). $[\alpha]_D = -15.1$ (c 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.54 (dd, J = 7.6, 1.6 Hz, Ar, 1H), 7.34-7.14 (m, Ar, 6H), 6.98 (t, J = 7.5 Hz, Ar, 1 H), 6.76

(d, J = 8.2 Hz, Ar, 1H), 5.73 (1 H, s, *CH*$(OCH_3)_2$), 5.63 (broad d, J = 8.1 Hz, NH, 1H), 4.21-4.05 (broad m, C*H*N, 1H), 3.98 (dd, J = 9.3, 2.6 Hz, C*H*HO, 1H), 3.84 (dd, J = 9.3, 3.8 Hz, C*H*HO, 1H), 3.47 (s, O*CH*$_3$, 3H), 3.29 (s, O*CH*$_3$, 3H), 3.10-2.94 (m, *CH*$_2$Ph, 2H), 1.43 (s, C(*CH*$_3$)$_3$, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C): δ 156.5, 155.5 (C=O and C-O), 138.1, 126.1 (quat.), 129.8, 129.5 (x2), 128.5 (x2), 127.6, 126.5, 120.7, 112.3 (aromatic CH), 99.4 (*C*H$(OCH_3)_2$), 79.3 (*C*$(CH3)_3$), 68.6 (*C*H_2O), 54.4 (O*C*H_3), 51.7 (OCH_3 and CHN), 38.2 (*C*H_2Ph), 28.4 (C(*C*$H_3)_3$). I.R. (ATR): ν_{max} 3346, 2978, 2930, 2897, 2827, 1700, 1606, 1590, 1522, 1494, 1455, 1442, 1388, 1365, 1337, 1284, 1244, 1203, 1164, 1125, 1096, 1047, 1033, 987, 973, 960, 921, 901, 881, 866, 850, 822, 780, 763, 742, 698, 670, 641, 623, 608 cm−1. HRMS (ESI+): found 402.2287 [Calcd for $C_{23}H_{32}NO_5^+$ $(M + H)^+$ 402.2280].

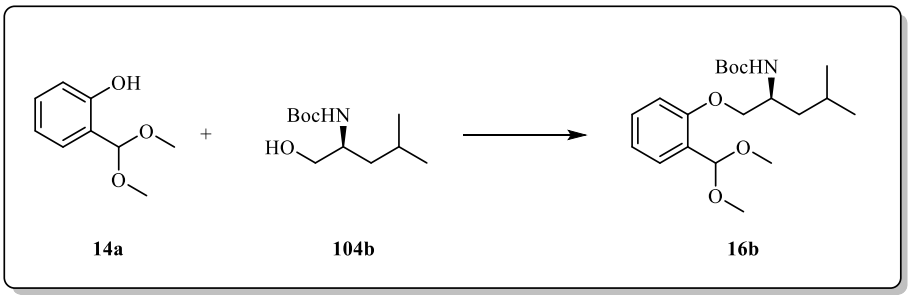
(*S*)-tert-Butyl 2-benzylaziridine-1-carboxylate 106.



106

Oil. R_f = 0.49 (PE: AcOEt 10:1). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C): δ 7.35-7.20 (m, 5H), 3.02-2.89 (m, C*H*N, 1H), 2.71-2.57 (m, C*H*$_2$N, 2H), 2.31 (d, J = 6.0 Hz, C*H*HPh, 1H), 2.03 (d, J = 3.6 Hz, C*H*HPh, 1H), 1.44 (s, C(C*H*$_3)_3$, 9H). This compound is known.[98]

Synthesis of (*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-4-methylbutan-2-yl)carbamate 16b.

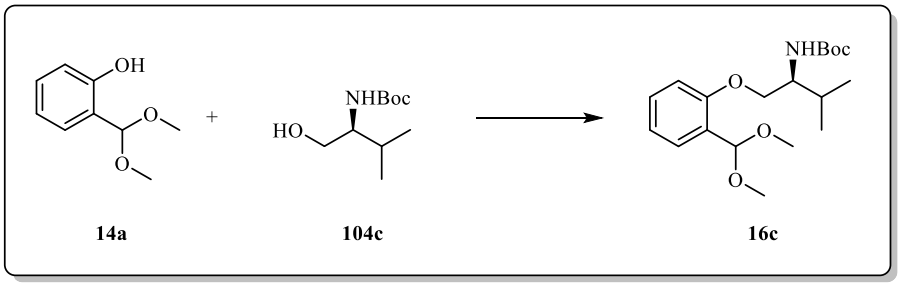


14a **104b** **16b**

It was prepared from salicylaldehyde and Boc-amino alcohol **104b** following the same procedure described for **16a**, but using stoichiometric quantities of **14a** and Boc-amino alcohol **104b**. The isolated yield of **16b** was 65% from salicylaldehyde. Chromatography was carried out with PE: AcOEt 30:1 →10:1. Oil. R_f = 0.34 (PE: AcOEt 30:1). $[\alpha]_D$ = + 50.3 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.52 (dd, J = 7.5, 1.5 Hz, Ar, 1H), 7.29 (td, J = 7.8, 1.5 Hz, Ar, 1H), 6.97 (td, J = 7.5, 1.2 Hz, Ar, 1H), 6.85 (dd, J = 8.1, 0.6 Hz, 1H), 5.65 (s, C*H*(OCH_3)2, 1H), 5.29 (broad d, J = 8.1 Hz, NH, 1H), 4.10-3.91 (m, C*H*N, C*H*HO, 3H), 3.43 (s, OC*H*3, 3H), 3.28 (s, OC*H*3, 3H), 1.80-1.45 (m, C*H*$_2$C*H*$(CH_3)_2$, 2H), 1.43 (s, C(C*H*$_3)_3$, 9H), 0.97 (d, J = 6.6 Hz, (C*H*$_3)_2$CH, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 156.6, 155.6 (*C*=O and *C*-O), 129.8, 127.5, 120.6, 112.2 (aromatic *C*H), 126.2 (quat.), 99.3 (*C*H$(OCH_3)_2$), 79.1 (*C*$(CH_3)_3$), 71.0 (*C*H_2O), 54.5 (O*C*H_3), 52.0 (O*C*H_3), 48.4 (*C*HN), 41.4 (*C*H_2*i*Pr), 28.4 (C(*C*$H_3)_3$), 24.9 (*C*H$(CH_3)_2$), 22.9, 22.5 (CH(*C*$H_3)_3$. I.R. (ATR): ν_{max} 3349, 2956, 2933, 2871, 2830, 1697, 1604, 1516, 1491, 1455, 1391, 1366, 1329, 1285, 1241, 1163, 1118, 1091, 1047,

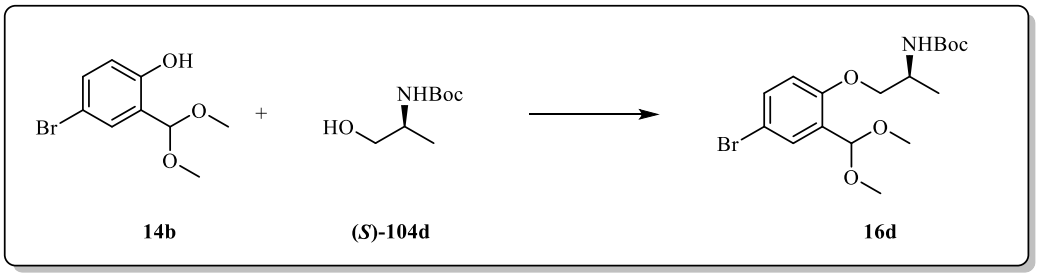
977, 910, 872, 847, 811, 754, 731, 672, 647, 610 cm^{-1}. HRMS (ESI+): found 368.2429 [Calcd for $C_{20}H_{34}NO_5^+$ $(M + H)^+$ 368.2437].

Synthesis of (*S*)-tert-Butyl (1-(2-(dimethoxymethyl)phenoxy)-3-methylpropan-2-yl)carbamate (16c).



It was prepared from salicylaldehyde and Boc-amino alcohol **104c** following the same procedure described for **16a**, but using 1.1 equiv. of **14a** relative to Boc-amino alcohol **104c**. The isolated yield of **16c** was 55% from **104c**. Chromatography was carried out with PE: AcOEt 16:1 →10:1. Oil. R_f = 0.25 (PE: AcOEt 16:1). $[\alpha]_D$ = −56.2 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.52 (dd, J = 7.6, 1.6 Hz, Ar, 1H), 7.29 (td, J = 7.5, 1.5 Hz, Ar, 1H), 6.98 (t, J = 7.5 Hz, Ar, 1H), 6.85 (d, J = 8.1 Hz, Ar, 1H), 5.64 (s, C*H*$(OCH_3)_2$, 1H), 5.43 (broad d, J = 9.0 Hz, N*H*, 1H), 4.21 (dd, J = 9.3, 2.8 Hz, C*H*HO, 1H), 3.92 (dd, J = 9.3, 3.8 Hz, C*H*HO, 1H), 3.73-3.60 (m, C*H*N, 1H,), 3.43 (s, OCH_3, 3H), 3.26 (s, OCH_3, 3H), 2.02 (octuplet, J = 7.1 Hz, C*H*$(CH_3)_2$, 1H), 1.43 (s, C(CH_3)$_3$, 9H), 1.02 (d, J = 6.9 Hz, (CH_3)CH, 3H), 1.00 (d, J = 6.9 Hz, (CH_3)CH, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 156.7, 155.9 (*C*=O and *C*-O), 129.8, 127.5, 120.5, 112.1 (aromatic *C*H), 126.2 (quat.), 99.3 (*C*H$(OCH_3)_2$), 79.0 (*C*$(CH_3)_3$), 69.1 (*C*H_2O), 55.6 (*C*HN), 54.5 (O*C*H_3), 51.7 (O*C*H_3), 30.2 (*C*H$(CH_3)_2$), 28.4 (C(*C*H_3)$_3$), 19.6, 19.3 (CH(*C*H_3)$_3$. I.R. (ATR): ν_{max} 3348, 2962, 2934, 2829, 1711, 1604, 1591, 1516, 1491, 1456, 1390, 1365, 1286, 1240, 1170, 1121, 1092, 1073, 1045, 1028, 979, 946, 911, 883, 867, 807, 755, 737, 703, 675, 650, 620, 610 cm^{-1}. HRMS (ESI+): found 354.2284 [Calcd for $C_{19}H_{32}NO_5^+$ $(M + H)^+$ 354.2280].

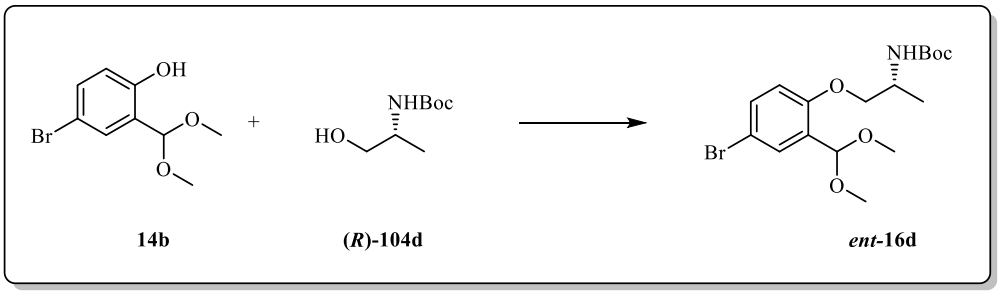
Synthesis of (*S*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-propane-2-yl)carbamate (16d).



It was prepared from 4-bromosalicylaldehyde and Boc-amino alcohol (*S*)-**104d** following the same procedure described for **16a**, but using 1.1 equiv. of **14b** relative to Boc-amino alcohol (*S*)-**104d**. The isolated yield of **16d** was 60% from **104d**. Chromatography was carried out with PE: AcOEt: CH_2Cl_2 8:1:1 →6:1:1. Oil. R_f = 0.37 (PE: AcOEt: CH_2Cl_2 8:1:1). $[\alpha]_D$ = −40.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.64 (d, J = 2.4 Hz, Ar, 1H), 7.38 (dd, J = 8.7, 2.7 Hz, Ar, 1H), 6.74 (d, J = 8.7 Hz, 1H), 5.61 (s, C*H*$(OCH_3)_2$, 1H), 5.26 (broad

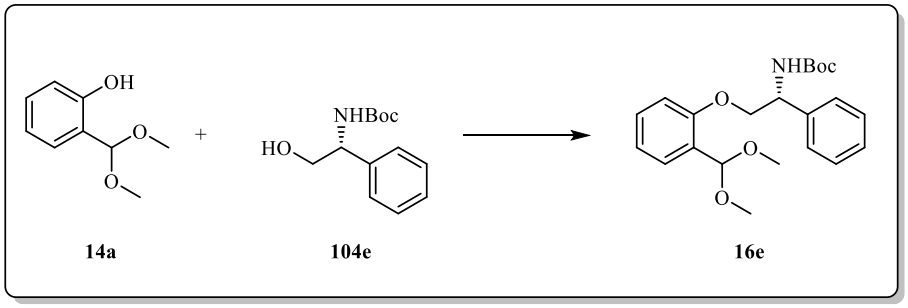
s, N*H*), 4.05 (broad s, C*H*NH, 1H), 4.01 (dd, J = 8.9, 2.8 Hz, C*H*HO, 1H), 3.90 (dd, J = 8.9, 4.3 Hz, C*H*HO, 1H), 3.41 (s, OCH_3, 3H), 3.28 (s, OCH_3, 3H), 1.44 (s, C(CH_3)$_3$, 9H), 1.31 (d, J = 6.6 Hz, CH_3CH, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 155.6, 155.3 (*C*=O and *C*-O), 132.4, 130.6, 114.0 (aromatic *C*H), 128.4, 113.3 (quat.), 98.5 (*C*H(OCH$_3$)$_2$), 79.3 (*C*(CH$_3$)$_3$), 72.2 (*C*H$_2$O), 54.3 (O*C*H$_3$), 52.0 (O*C*H$_3$), 45.9 (*C*HN), 28.4 (C(*C*H$_3$)$_3$), 18.2 (*C*H$_3$CH). I.R. (ATR): ν_{max} 3350, 2976, 2933, 2830, 1695, 1595, 1514, 1487, 1457, 1404, 1391, 1365, 1266, 1242, 1164, 1133, 1099, 1053, 980, 912, 875, 854, 806, 781, 752, 734, 677, 657, 645, 616 cm^{-1}. HRMS (ESI+): found 404.1075 [Calcd for $C_{17}H_{27}BrNO_5^+$ $(M + H)^+$ 404.1073].

Synthesis of (*R*)-*tert*-Butyl (1-(2-(dimethoxymethyl)phenoxy)-propane-2-yl)carbamate (*ent*-16d).



It was prepared exactly as for **16d**, but starting from (*R*)-**104d**. $[\alpha]_D$ = +39.9 (c 1.0, $CHCl_3$). The other spectroscopical data were identical to those of **16d**.

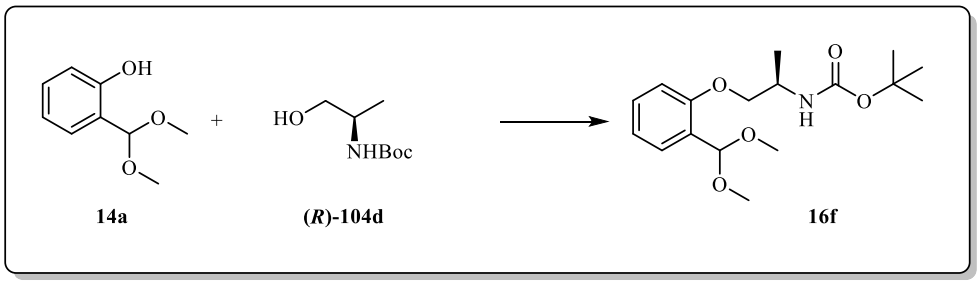
Synthesis of (*R*)-*tert*-Butyl (2-(2-(dimethoxymethyl)phenoxy)-1-phenylethan-1-yl)carbamate (16e).



It was prepared from salicylaldehyde and Boc-amino alcohol **104e** following the same procedure described for **16a**, but using 1.1 equiv. of **14a** relative to Boc-amino alcohol **104e**. The isolated yield of **16e** was 42% from **104e**. Chromatography was carried out with PE: AcOEt 8:1 →6:1. Oil. R_f = 0.20 (PE: AcOEt 8:1). $[\alpha]_D$ = −33.5 (c 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.49 (dd, J = 7.6, 1.6 Hz, Ar, 1H), 7.46-7.22 (m, Ar, 6H), 6.97 (t, J = 7.5 Hz, Ar, 1H), 6.82 (d, J = 8.4 Hz, Ar, 1H), 6.12 (broad s, N*H*), 5.54 (s, C*H*(OCH$_3$)$_2$, 1H), 5.09 (broad s, C*H*NH, 1H), 4.32-4.15 (m, CH_2O, 2H), 3.40 (s, OCH_3, 3H), 3.28 (s, OCH_3, 3H), 1.43 (s, C(CH_3)$_3$, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 156.3, 155.5 (*C*=O and *C*-O), 140.2, 126.5 (quat.), 129.8, 128.5 (x2), 127.6, 127.4, 126.8 (x2), 120.9, 112.4 (aromatic *C*H), 99.6 (*C*H(OCH$_3$)$_2$), 79.5 (*C*(CH$_3$)$_3$), 72.0 (*C*H$_2$O), 54.6 (O*C*H$_3$), 54.1 (*C*HN), 52.0 (O*C*H$_3$), 28.4 (C(*C*H$_3$)$_3$). I.R. (ATR): ν_{max} 3335, 2977, 2933, 2830, 1706, 1604, 1591, 1515, 1491, 1454, 1391, 1366, 1284, 1239, 1164, 1121, 1092, 1070, 1047, 979, 947, 902, 867, 794,

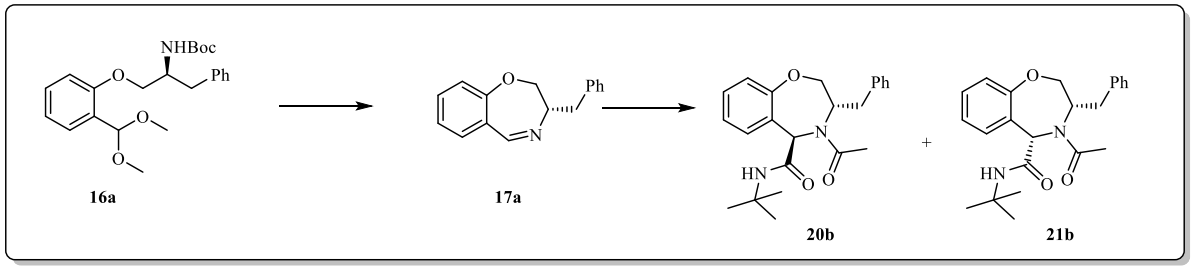
751, 699, 666, 633 cm^{-1}. HRMS (ESI+): found 388.2119 [Calcd for $C_{22}H_{30}NO_5^+$ $(M + H)^+$ 388.2124].

Synthesis of *tert*-butyl (*R*)-(1-(2-(dimethoxymethyl)phenoxy)propan-2-yl)carbamate (16f)



It was prepared from salicylaldehyde and Boc-amino alcohol (*R*)-**104d** following the same procedure described for **16a**, but using 1.1 equiv. of **14a** relative to Boc-amino alcohol (*R*)-**104d**. The isolated yield of X was 58% from **104d**. Chromatography was carried out with PE: AcOEt: CH_2Cl_2 8:1:1. Colorless Oil. R_f = 0.30 (PE: AcOEt: CH_2Cl_2 8:1:1). $[\alpha]_D$ = −42.7 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, Chloroform-d) δ 7.53- 7.28 (m, Ar, 1H), 7.27-7.26 (m, Ar, 1H), 6.98-6.95 (m, Ar, 1H), 6.87-6.84 (m, Ar, 1H), 5.67 (s, *CH*OCH_3,1H), 5.36 (bs, NH, 1H), 4.10-4.00 (m, *CH*CH3, OC*H*H, 2H), 3.94 (dd, J= 9.07, 4.20 Hz, 3.43 (s, O*CH*$_3$, 3H), 3.3 (s, O*CH*$_3$, 3H), 1.44 (s, ^{t}Butyl, 3H), 1.33 (d, J= 6.72 Hz, CH*CH*$_3$, 3H).^{13}C NMR (75 MHz, Chloroform-d) δ 156.5, 155.4 (quat.), 129.8, 127.5, 126.2, 120.6, 112.19, 99.4 (aromatic CH), 71.9 (OCH_2), 54.3 (O*CH*$_3$), 52.1 (O*CH*$_3$), 46.0 (*CH*CH_3), 28.4 (^{t}Butyl), 18.2 (CH*CH*$_3$). I.R. (ATR): ν_{max}: 3343, 2976, 2933, 2829, 1694, 1603, 1491, 1454, 1365, 1285, 1240, 1162, 1121, 1093, 1047, 977, 905, 752.

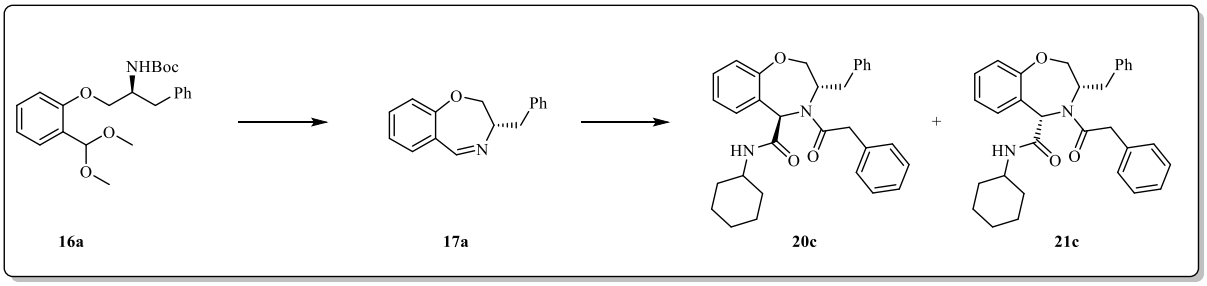
Typical procedure for the synthesis of Ugi-Joullié adducts: (3*S*,5*R*)-4-acetyl-3-benzyl-*N*-(tert-butyl)-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (20b).



Acetal **16a** (312.4 mg, 778 µmol) was dissolved in CH_2Cl_2 (3.0 mL) and treated with 37% aqueous HCl (640 µL, 7.73 mmol). The mixture was stirred at rt for 5 h. Then it was diluted with CH_2Cl_2, and cautiously treated with 5% aqueous Na_2CO_3 (25 mL). After checking that pH > 9, the two phases were separated, washed with brine, and evaporated to dryness. The resulting crude imine **17a** (oil) was taken up in dry methanol (3.90 mL), and treated with acetic acid (53 µL, 927 µmol), and *tert*-butyl isocyanide (106 µl, 937 µmol). The mixture was stirred at rt for 45 h and evaporated to dryness. It was taken up in AcOEt, washed with saturated aqueous $NaHCO_3$ (to remove excess carboxylic acid), evaporated, and chromatographed (PE: AcOEt 2:1) to give pure **20b** (237 mg, 80%). The ratio **20b**: **21b** was determined by HPLC on the crude product and resulted = 96:4. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.38 ml/min. Temp: 26°C. Eluent: H_2O: CH_3CN 55:45.

Detection: UV 220 nm. R_t of **20b**: 13.62. R_t of **21b**: 14.41. Minor diastereomer **21b** was recognized using a MS (ESI) detector. White solid. R_f = 0.24 (PE: AcOEt 2:1) (R_f of **20b** = 0.31). $[\alpha]_D$ = +10.0 (c 1.06, $CHCl_3$). M.p. = 119.7-122.0 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.57 (dd, J = 7.7, 1.6 Hz, Ar, 1H), 7.36-7.16 (m, Ar, 6H), 7.00 (t, J = 8.2 Hz, Ar, 2H), 6.47 (broad s, N*H*, 1H), 5.66 (broad s, C*H*C=O, 1H), 4.77 (broad d, J = 11.1 Hz, C*H*HO, 1H), 4.55 (broad s, C*H*N, 1H), 4.03 (dd, J = 13.2, 4.8 Hz, C*H*HO, 1H), 2.79 (dd, J = 13.4, 5.9 Hz, C*H*HPh, 1H), 2.65-2.48 (m, C*H*HPh, 1H), 2.06 (s, CH_3C=O, 3H),1.22 (s, C(CH_3)$_3$, 9H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 169.8, 168.8 (*C*=O), 155.6 (aromatic *C*-O), 137.6, 121.4 (quat.), 132.1, 129.6, 128.4 (x2), 127.8 (x2), 125.8, 120.9, 118.8 (aromatic *C*H), 66.6 (*C*H_2O), 62.8 (broad) (*C*HC=O), 57.5 (broad) (*C*HN), 50.2 (*C*(CH$_3$)$_3$), 36.4 (*C*H_2Ph), 27.8 (C(*C*H_3)$_3$), 21.2 (*C*H_3C=O). I.R. (ATR): ν_{max} 3410, 3314, 3067, 3034, 2966, 2928, 2870, 1671, 1639, 1607, 1580, 1563, 1509, 1494, 1453, 1416, 1391, 1366, 1352, 1332, 1305, 1288, 1267, 1249, 1224, 1193, 1172, 1157, 1125, 1115, 1086, 1052, 1028, 1007, 973, 937, 908, 885, 871, 862, 827, 802, 752, 731, 719, 700, 665, 644, 631, 616, 603 cm^{-1}. HRMS (ESI+): found 381.2171 [Calcd for $C_{23}H_{29}N_2O_3^+$ $(M + H)^+$ 381.2178].

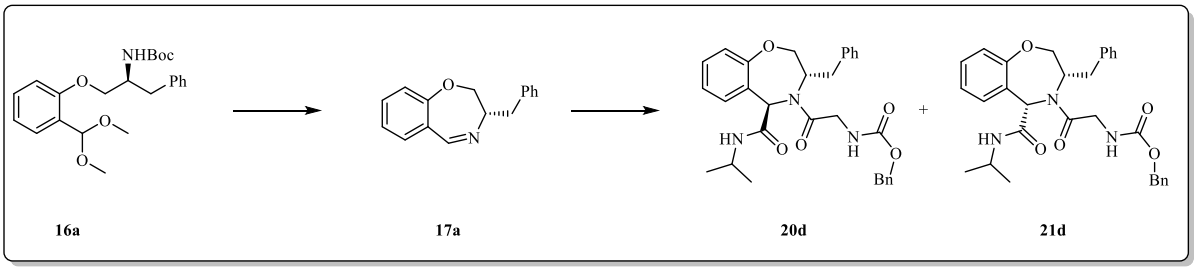
Synthesis of (*3S*,*5R*)-3-Benzyl-*N*-(cyclohexyl)-4-phenylacetyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20c).



It was prepared in 65% overall yield from (*S*)-**16a**, phenylacetic acid and cyclohexyl isocyanide, following the typical procedure described for **20b**. Chromatography was carried out with PE: AcOEt: CH_2Cl_2 5: 1: 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **20c** plus some fractions contaminated with little **21c**. The overall yield was 65%. The calculated yield of **20c** is therefore 62%. The d.r. was = 94: 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 30:70. Detection: UV 220 nm. R_t of **20c**: 21.25. R_t of **21c**: 20.43. Minor diastereomer **21c** was recognized using a MS (ESI) detector. White solid. R_f = 0.21 (PE: AcOEt: CH_2Cl_2 5 : 1 : 1) (R_f of **21c** = 0.24). $[\alpha]_D$ = +9.0 (c 1.0, $CHCl_3$). M.p. = 157.8-159.9 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.42 (broad s, Ar, 1H), 7.36-7.15 (m, Ar, 11H), 7.05-6.95 (m, Ar, 2H), 6.80 (broad d, J = 6.6 Hz, N*H*, 1H), 5.72 (s, C*H*C=O, 1H), 4.75 (broad d, J = 12.3 Hz, C*H*HO, 1H), 4.61 (broad s, C*H*N, 1H), 4.02 (dd, J = 13.3, 4.6 Hz, C*H*HO, 1H), 3.84 (d, J = 15.6 Hz, C*H*HC=O, 1H), 3.67-3.50 (m, C*H*C=O, C*H*NH, 2H), 2.80 (dd, J = 13.2, 6.0 Hz, C*H*HPh, 1H), 2.65-2.48 (m, C*H*HPh, 1H), 1.80-1.45 (m, CH_2 cyclohexyl, 5H), 1.35-1.05 (m, CH_2 cyclohexyl, 5H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 170.2 168.4 (*C*=O), 155.6 (broad) (aromatic *C*-O), 137.5, 135.1, 121.3 (quat.), 132.1, 129.6 (x2), 128.5 (x2), 128.4 (x2), 127.8 (x2), 127.6, 125.83, 125.76, 121.0, 118.7 (aromatic *C*H), 66.7 (broad) (*C*H_2O), 65.9 (broad) (*C*HC=O), 57.3 (broad) (*C*HN), 47.7 (*C*HNH), 39.4 (*C*H_2C=O, hidden by DMSO signal, visible at qHSQC), 36.3 (broad) (*C*H_2Ph), 31.2 (x2), 24.6, 23.7, 23.6 (*C*H_2 cyclohexyl). I.R. (ATR): ν_{max} 3271, 3023, 2977, 2940, 2920, 2855,

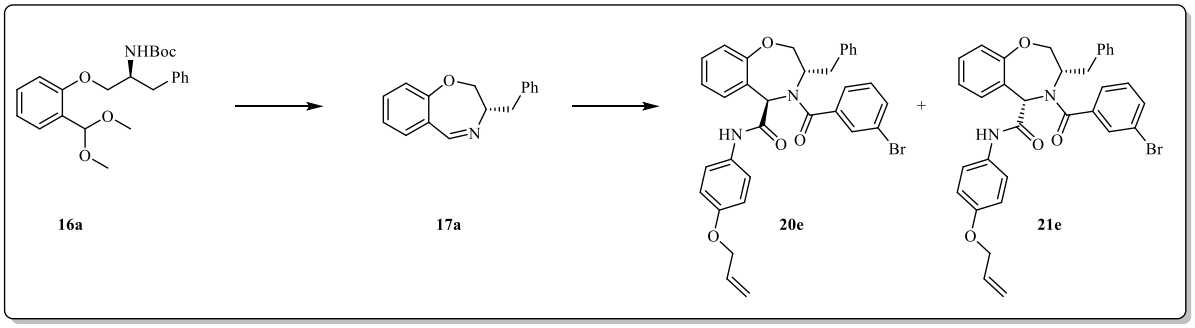
1656, 1633, 1604, 1582, 1525, 1492, 1451, 1416, 1360, 1343, 1319, 1306, 1289, 1270, 1250, 1222, 1193, 1150, 1115, 1094, 1076, 1060, 1029, 1012, 981, 968, 957, 935, 907, 893, 884, 875, 853, 826, 809, 781, 762, 749, 720, 696, 640, 619 cm^{-1}. HRMS (ESI+): found 483.2654 [Calcd for $C_{31}H_{35}N_2O_3^+$ $(M + H)^+$ 483.2648].

Synthesis of (*3S,5R*)-3-Benzyl-4-(2-((benzyloxycarbonyl)amino)acetyl)-*N*-(isopropyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20d).



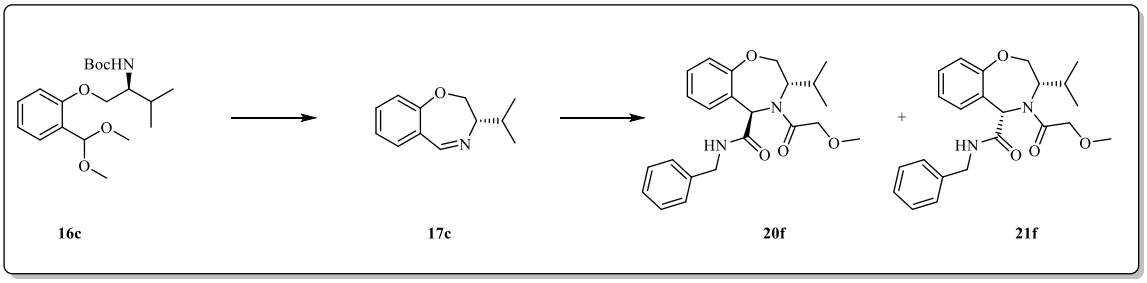
It was prepared in 80% overall yield from (*S*)-**16a**, *N*-benzyloxycarbonyl glycine and isopropyl isocyanide, following the typical procedure described for **20b**. Chromatography was carried out with PE: AcOEt 2: 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **20d** plus some fractions contaminated with little **21d**. The overall yield was 80%. The calculated yield of **20d** is therefore 74.4%. The d.r. was = 94: 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 1 ml/min. Temp: 26°C. Eluent: H_2O: CH_3CN 50:50. Detection: UV 220 nm. R_t of **20d**: 20.55. R_t of **21d**: 21.68. Minor diastereomer **21d** was recognized using a MS (ESI) detector. White solid. R_f = 0.12 (PE / AcOEt 2: 1) (R_f of **21d** = 0.17). $[\alpha]_D$ = −19.7 (c 1.0, $CHCl_3$). M.p. = 70.0-72.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.56 (d, J = 7.5 Hz, Ar, 1H), 7.40-7.17 (m, Ar, 11H), 7.01 (t, J = 7.5 Hz, Ar, 2H), 7.00-6.90 (m, N*H*CH_2, 1H), 6.89 (broad d, J = 7.2 Hz, N*H*CH, 1H), 5.66 (s, C*H*C=O, 1H), 5.08 (s, PhC*H*$_2$O, 2H), 4.76 (broad d, J = 12.9 Hz, C*H*HO, 1H), 4.54 (broad s, C*H*N, 1H), 4.16 (dd, J = 16.6, 5.6 Hz, C*H*HNH, 1H), 4.01 (dd, J = 13.2, 4.5 Hz, C*H*HO, 1H), 3.93-3.77 (m, C*H*NH, C*H*HNH, 2H), 2.82 (dd, J = 13.4, 5.1 Hz, C*H*HPh, 1H), 2.62-2.48 (m, C*H*HPh, 1H), 1.08 (d, J = 6.6 Hz, C*H*$_3$, 3H), 1.00 (d, J = 6.6 Hz, C*H*$_3$, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 168.6 168.2 (*C*=O), 155.7, 155.5 (*C*=O urethane and aromatic *C*O), 137.4, 136.6, 121.1 (quat.), 132.4, 129.6, 128.4 (x2), 127.8 (x2), 127.7 (x2), 127.1, 126.9 (x2), 125.9, 120.9, 118.7 (aromatic *C*H), 66.0 (broad) (*C*H_2O), 65.1 (Ph*C*H_2O), 61.6 (broad) (*C*HC=O), 57.2 (*C*HN), 42.3 (*C*H_2NH), 40.8 (*C*HNH), 36.3 (broad) (*C*H_2Ph), 21.3 (*C*H_3). I.R. (ATR): ν_{max} 3410, 3321, 3064, 3031, 2971, 2935, 1715, 1648, 1606, 1581, 1510, 1493, 1453, 1424, 1387, 1366, 1347, 1241, 1220, 1156, 1115, 1084, 1049, 1030, 1010, 929, 912, 892, 871, 826, 797, 749, 697, 658, 638 cm^{-1}. HRMS (ESI+): found 516.2490 [Calcd for $C_{30}H_{34}N_3O_5^+$ $(M + H)^+$ 516.2498].

Synthesis of (*3S,5R*)-*N*-(4-Allyloxyphenyl)-3-benzyl-4-(3-bromobenzoyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20e).



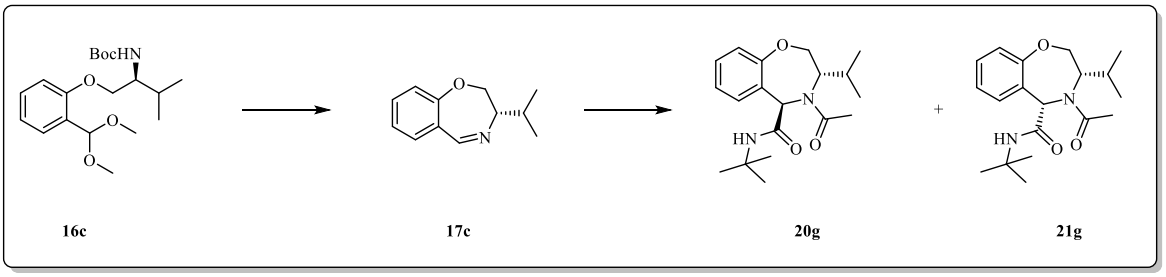
A solution of N-(4-(allyloxy)phenyl)formamide (100 mg, 564 µmol)[99] in dry CH_2Cl_2 (0,84 mL) was cooled at 0°C and treated with Burgess reagent (Methyl *N*-(triethylammoniosulfonyl)carbamate inner salt161.2, mg (676 µmol). The mixture was stirred at 0°C for 3h, then further 66.0 mg (276 µmol) of Burgess Reagent were added to the mixture. After 10 min. the mixture was allowed to reach room temperature and stirred for 2h. This mixture was then added to a solution of imine **17a** (400 µmol) in MeOH (1.5 mL), prepared as described above for the synthesis of **20b**. Finally, 3-bromobenzoic acid (112 mg, 557 µmol mmol) was added at this mixture. The mixture was stirred at room temperature for 48h and then 30 °C overnight. The solvent was evaporated under reduced pressure and the crude product was purified by chromatography (PE: AcOEt 5:1) to give pure **20e** (128.8 mg, 54%). The d.r. was = 93: 7 by HPLC of the crude product. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.34 ml/min. Temp: 25°C. Eluent: H_2O: CH_3CN 40:60 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **20e**: 13.33. R_t of **21e**: 14.00. Minor diastereomer **21e** was recognized using a MS (ESI) detector. The overall yield, calculated from the d.r., was 58%. White solid. R_f = 0.13 (PE / AcOEt 2: 1). $[\alpha]_D$ = +57.0 (c 1.0, $CHCl_3$). M.p. = 148.6-150.7 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 9.17 (s, N*H*, 1H), 7.64 (ddd, J = 8.1, 1.8, 1.0 Hz, Ar, 2H), 7.44-7.18 (m, Ar, 9H), 7.10 (td, J = 7.5, 1.2 Hz, Ar, 1H), 7.05 (dd, J = 8.1, 0.9 Hz, Ar, 1H), 7.01-6.92 (m, Ar, 2H), 6.88 (d, J = 9.0 Hz, Ar, 2H), 6.02 (ddt, J = 17.2, 10.5, 5.2 Hz, C*H*=CH_2, 1H), 5.81 (broad s, C*H*C=O, 1H), 5.37 (dq, J = 17.2, 1.6 Hz, CH=C*H*H, 1H), 5.23 (dq, J = 10.5, 1.5 Hz, CH=C*H*H, 1H), 4.95 (dd, J = 12.3, 1.8 Hz, C*H*HO, 1H), 4.53 (dt, J = 5.4, 1.5 Hz, C*H*$_2$CH=CH_2, 2H), 4.44 (broad s, C*H*N, 1H), 4.13 (dd, J = 13.0, 4.0 Hz, C*H*HO, 1H), 2.73 (dd, J = 13.2, 7.3 Hz, C*H*Ph, 1H), 2.62 (dd, J = 13.2, 8.4 Hz, C*H*HPh, 1H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ169.1 167.4 (*C*=O), 155.6, 154.4, 138.0, 137.2, 131.2, 121.7, 121.2 (quat.), 133.3 (*C*H=CH_2), 131.9, 131.7, 130.1, 130.0, 128.5 (x2), 128.3, 127.8 (x2), 125.9, 124.6, 121.8, 121.4 (x2), 119.6, 114.4 (x2) (aromatic *C*H), 116.5 (CH=*C*H_2), 68.2 (*C*H_2CH=CH_2), 68.1 (broad) (*C*H_2O), 63.4 (broad) (*C*HC=O), 58.4 (broad) (*C*HN), 37.0 (broad) (*C*H_2Ph). I.R. (ATR): ν_{max} 3314, 3062, 2945, 2906, 2026, 1672, 1646, 1606, 1578, 1563, 1509, 1488, 1446, 1414, 1386, 1353, 1330, 1305, 1278, 1256, 1211, 1171, 1148, 1114, 1094, 1085, 1069, 1061, 1027, 1007, 967, 934, 914, 897, 887, 864, 824, 807, 752, 730, 709, 703, 682, 665, 649, 637, 605 cm^{-1}. HRMS (ESI+): found 597.1396 [Calcd for $C_{33}H_{30}BrN_2O_4^+$ $(M + H)^+$ 597.1389].

Synthesis of (*3S*,*5R*)-*N*-(Benzyl)-3-*iso*-propyl-4-(methoxyacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20f).



It was prepared in 53% yield from (*S*)-**16c**, methoxyacetic acid and benzyl isocyanide, following the typical procedure described for **20b**. However, in this case, the Ugi-Joullié step reaction was carred out at 40°C. Chromatography was carried out with PE: AcOEt 1: 1, affording a complete separation of the two diastereomers. The overall yield was 56%. The d.r. was = 94: 6 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 30:70 + 1% TFA. Detection: UV 220 nm. R_t of **20f**: 6.02. R_t of **21f**: 5.49. Minor diastereomer **21f** was recognized using a MS (ESI) detector. Oil. R_f = 0.35 (PE: AcOEt 1: 1) (R_f of **21f** = 0.46). $[\alpha]_D$ = −42.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.80 (s, N*H*, 1H), 7.48 (d, J = 6.6 Hz, Ar, 1H), 7.31-7.14 (m, Ar, 6H), 6.99 (td, J = 7.5, 1.2 Hz, Ar, 1H), 6.91 (dd, J = 8.1, 1.1 Hz, Ar, 1H), 5.62 (s, C*H*C=O, 1H), 4.76 (broad d, J = 12.3 Hz, C*H*HO, 1H), 4.37 (dd, J = 13.2, 4.8 Hz, C*H*HO, 1H), 4.31 (broad t, J = 5.4 Hz, CH_2NH, 2H), 4.29 (J = 14.2 Hz, C*H*HOMe, 1H), 4.11 (broad s, C*H*N, 1H), 4.01 (J = 14.2 Hz, C*H*HOMe, 1H), 3.31 (s, CH_3O, 3H), 1.59 (d of heptuplets, J = 9.9, 6.6 Hz, C*H*$(CH_3)_3$, 1H), 0.88 (d, J = 6.6 Hz, CH_3CHCH_3, 3H), 0.75 (d, J = 6.8 Hz, CH_3CHCH_3, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 169.3 (x2) (*C*=O), 156.0, 138.7, 122.3 (quat.), 131.6, 129.5, 127.5 (x2), 126.4 (x2), 126.0, 121.3, 119.1 (aromatic *C*H), 70.6 (*C*H_2OMe), 68.1 (broad) (*C*H_2O), 62.0 (*C*HC=O), 59.8 (broad) (*C*HN), 57.8 (O*C*H_3), 42.3 (*C*H_2NH), 28.5 (*C*H$(CH_3)_2$), 19.3, 18.8 (*C*H_3). I.R. (ATR): ν_{max} 3314, 3062, 3031, 2964, 2931, 2873, 2825, 1653, 1605, 1580, 1516, 1493, 1453, 1424, 1390, 1367, 1320, 1248, 1218, 1198, 1156, 1124, 1107, 1080, 1028, 965, 948, 860, 838, 750, 731, 698, 640, 605 cm^{-1}. HRMS (ESI+): found 397.2135 [Calcd for $C_{23}H_{29}N_2O_4^+$ $(M + H)^+$ 397.2127].

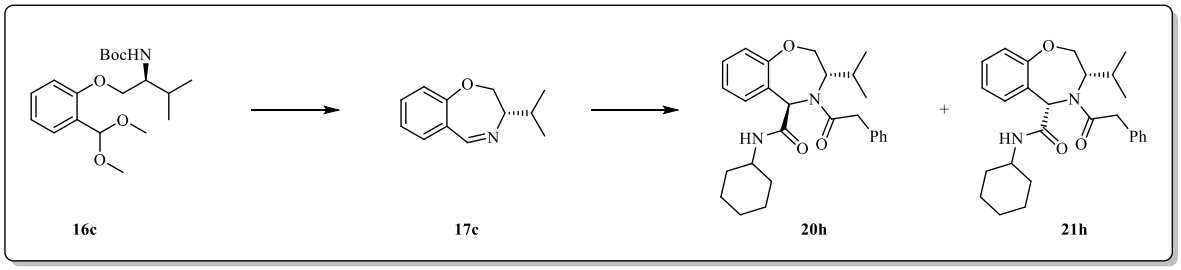
Synthesis of (*3S*,*5R*)-4-(Acetyl)-*N*-(*tert*-butyl)-3-*iso*-propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20g).



It was prepared in 52% yield from (*S*)-**16c**, acetic acid and *tert*-butyl isocyanide, following the typical procedure described for **20b**. The reaction was in this case incomplete and also 6% of starting material was recovered. Chromatography was carried out with CH_2Cl_2: AcOEt 4: 1, affording a complete separation of the two diastereomers. The minor diastereomer **21g** was

not detected by HPLC-MS or NMR. The d.r. was thus supposed to be > 97: 3. HPLC conditions: C6-Phenyl column 150 x 3 mm, 3 µm. Flow: 0.38 ml/min. Temp: 26°C. Eluent: H_2O: CH_3CN 60:40. Detection: UV 220 nm. R_t of **20g**: 11.66. White solid. R_f = 0.28 (CH_2Cl_2: AcOEt 4: 1). $[\alpha]_D$ = −9.4 (c 0.9, $CHCl_3$). M.p: 104.5-107.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 7.46 (dd, J = 7.6, 1.4 Hz, Ar, 1H), 7.25 (td, J = 8.0, 1.6, Ar, 1H), 6.98 (td, J = 7.5, 1.1 Hz, Ar, 1H), 6.90 (dd, J = 8.1, 1.0, Ar, 1H), 6.62 (broad s, N*H*, 1H), 5.49 (s, C*H*C=O, 1H), 4.68 (dd, J = 12.5, 3.7 Hz, C*H*HO, 1H), 4.35 (dd, J = 12.5, 5.8 Hz, C*H*HO, 1H), 4.12 (broad s, C*H*N, 1H), 2.10 (s, C*H*$_3$C=O, 3H), 1.71 (d of heptuplets, J = 9.9, 6.6 Hz, C*H*(CH_3)$_3$, 1H), 1.26 (s, C(C*H*$_3$)$_3$, 9H), 0.90 (d, J = 6.6 Hz, C*H*$_3$CHC*H*$_3$, 3H), 0.79 (d, J = 6.8 Hz, C*H*$_3$CHC*H*$_3$, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 170.3, 168.4 (*C*=O), 155.9, 123.3 (quat.), 130.7, 129.1, 121.2, 119.2 (aromatic *C*H), 68.4 (*C*H_2O), 63.3 (broad) (*C*HC=O), 59.9 (very broad, barely visible) (*C*HN), 50.1 (*C*NH), 28.4 (*C*H(CH_3)$_2$), 27.8 (C(*C*H_3)$_3$), 21.7 (*C*H_3C=O), 19.3, 18.9 (*C*H_3). I.R. (ATR): ν_{max} 3332, 2965, 2933, 2874, 1980, 1668, 1640, 1607, 1583, 1529, 1496, 1451, 1413, 1392, 1365, 1346, 1331, 1303, 1289, 1266, 1250, 1218, 1116, 1088, 1041, 979, 945, 900, 890, 858, 841, 812, 755, 746, 689, 654, 631, 621 cm^{-1}. HRMS (ESI+): found 333.2176 [Calcd for $C_{19}H_{29}N_2O_3^+$ $(M + H)^+$ 333.2178].

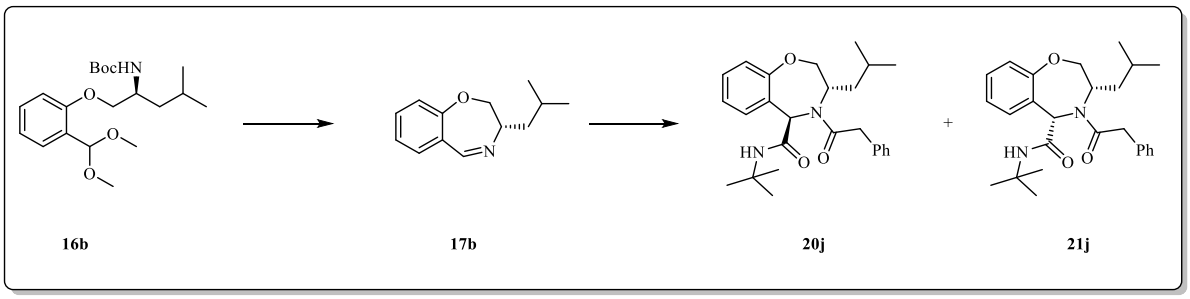
Synthesis of (*3S,5R*)-*N*-(Cyclohexyl)-3-*iso*-propyl-4-(phenylacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20h).



It was prepared in 79% yield from (*S*)-**16c**, phenylacetic acid and cyclohexyl isocyanide, following the typical procedure described for **20b**. However, in this case, the Ugi-Joullié step reaction was carried out at rt for 64 h. Chromatography was carried out with PE: CH_2Cl_2: AcOEt 3: 1: 1, affording a complete separation of the two diastereomers. The overall yield was 82%. The d.r. was = 96: 4 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 30:70. Detection: UV 220 nm. R_t of **20h**: 15.14. R_t of **21h**: 13.89. Minor diastereomer **21h** was recognized using a MS (ESI) detector. White solid. R_f = 0.42 (PE: CH_2Cl_2: AcOEt 3: 1: 1). $[\alpha]_D$ = −72.8 (c 1.0, $CHCl_3$). M.p.: 65.0-67.2 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ 7.39 (d, J = 7.8 Hz, Ar, 1H), 7.33-7.19 (m, Ar, 6H), 6.98 (t, J = 7.5 Hz, Ar, 1H), 6.89 (d, J = 8.1, Ar, 1H), 6.78 (broad s, N*H*, 1H), 5.61 (s, C*H*C=O, 1H), 4.63 (dd, J = 12.5, 3.0 Hz, C*H*HO, 1H), 4.35 (dd, J = 12.5, 5.5 Hz, C*H*HO, 1H), 4.20 (broad s, C*H*N, 1H), 3.86 (d, J = 15.6 Hz, C*H*HPh, 1H), 3.71 (d, J = 15.6 Hz, C*H*HPh, 1H), 3.63 (broad m, C*H*NH, 1H), 1.83-1.48 (m, C*H*(CH_3)$_2$ and C*H*$_2$ cyclohexyl, 6H), 1.38-1.10 (m, C*H*$_2$ cyclohexyl, 5H), 0.89 (d, J = 6.6 Hz, C*H*$_3$CHC*H*$_3$, 3H), 0.75 (d, J = 6.8 Hz, C*H*$_3$CHC*H*$_3$, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 171.3, 168.1 (*C*=O), 156.0, 135.4, 123.3 (quat.), 130.8, 129.3, 128.7 (x2), 127.6 (x2), 125.8, 121.4, 119.3 (aromatic *C*H), 68.6 (*C*H_2O), 62.5 (broad) (*C*HC=O), 60.4 (very broad) (*C*HN), 47.6 (*C*HNH), 39.9 (*C*H_2Ph), 31.43, 31.37, 24.6, 23.7, 23.6 (*C*H_2 cyclohexyl), 28.5 (*C*H(CH_3)$_2$), 19.3, 18.8 (*C*H_3). I.R. (ATR): ν_{max} 3418, 3320, 3064, 3031, 2930, 2854, 1647, 1604, 1581, 1510, 1493, 1450, 1408, 1387, 1367, 1348, 1319, 1248, 1217, 1153, 1113, 1080,

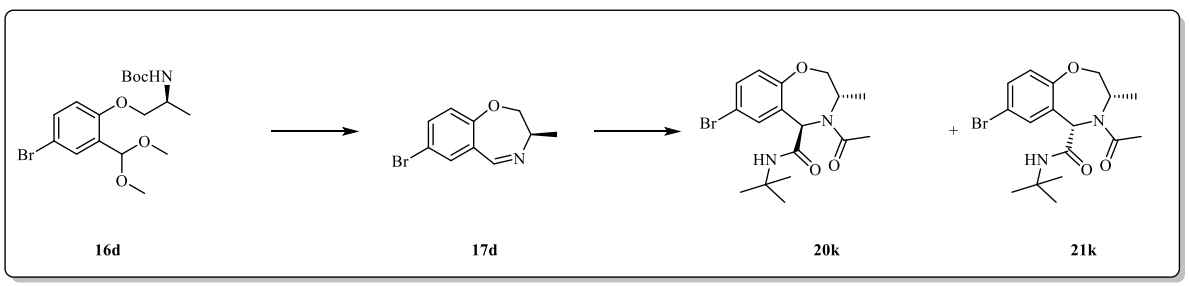
1031, 949, 891, 855, 810, 795, 757, 747, 719, 696, 641 cm^{-1}. HRMS (ESI+): found 435.2639 [Calcd for $C_{27}H_{35}N_2O_3^+$ $(M + H)^+$ 435.2648].

Synthesis of (*3S,5R*)-3-*iso*-Butyl-*N*-(*tert*-butyl)-4-(phenylacetyl)-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20j).



It was prepared in 57% overall yield from (*S*)-**16b**, phenylacetic acid and *tert*-butyl isocyanide, following the typical procedure described for **20b**. The reaction under these conditions was not complete. Chromatography was carried out with PE: AcOEt 5: 1. Separation of the two diastereomers was not complete. We obtained fractions with pure **20j** plus some fractions contaminated with little **21j**. The overall yield was 57%. The calculated yield of **20j** is therefore 54%. The d.r. was 96: 4 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 30:70 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **20j**: 18.25. R_t of **21j**: 16.23. Minor diastereomer **26e** was recognized using a MS (ESI) detector. Oil. R_f = 0.22 (PE: AcOEt 5: 1) (R_f of **21j** = 0.25). $[\alpha]_D$ = +12.2 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.26-7.07 (m, Ar, 7H), 6.32 (s, N*H*, 1H), 5.52 (s, C*H*C=O, 1H), 4.59 (d, J = 12.9 Hz, C*H*HO, 1H), 4.36 (broad s, C*H*N, 1H), 4.12 (dd, J = 13.2, 5.2 Hz, C*H*HO, 1H), 3.74 (d, J = 15.6 Hz, C*H*HPh, 1H), 3.57 (d, J = 15.6 Hz, C*H*HPh, 1H), 1.51 (nonuplet, J = 6.6 Hz, C*H*$(CH_3)_2$, 1H), 1.17 (t, J = 6.9 Hz, CH_2*i*Pr, 2H), 1.11 (s, C(CH_3)$_3$, 9H), 0.74 (d, J = 6.6 Hz, CH_3CHCH_3, 3H), 0.67 (d, J = 6.6 Hz, CH_3CHCH_3, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 170.3 168.7 (*C*=O), 155.7, 135.2, 121.6 (quat.), 131.6, 129.3, 128.5 (x2), 127.6 (x2), 125.8, 120.8, 118.6 (aromatic *C*H), 67.6 (*C*H_2O), 62.3 (broad) (*C*HC=O), 54.0 (broad) (*C*HN), 50.2 (*C*H_2*i*Pr), 39.6 (*C*H_2Ph), 27.7 (C(*C*H_3)$_3$), 24.3 (*C*H$(CH_3)_2$), 22.7, 21.2 (*C*H_3). I.R. (ATR): ν_{max} 3413, 3331, 3063, 3030, 2959, 2930, 2870, 1683, 1644, 1604, 1580, 1508, 1492, 1452, 1411, 1393, 1365, 1348, 1309, 1264, 1248, 1219, 1168, 1144, 1115, 1096, 1076, 1057, 1030, 1004, 957, 869, 823, 804, 758, 721, 695, 634 cm^{-1}. HRMS (ESI+): found 423.2641 [Calcd for $C_{26}H_{36}N_2O_3^+$ $(M + H)^+$ 423.2648].

Synthesis of (*3S,5R*)-4-(3-Acetyl)-7-bromo-*N*-(*tert*-butyl)-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20k).

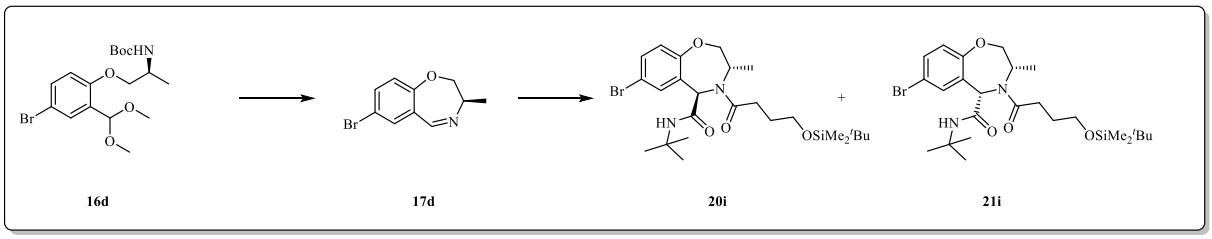


It was prepared in 68% yield from (*S*)-**16d**, acetic acid and *tert*-butyl isocyanide, following the typical procedure described for **20b**. However, in this case, during Ugi-Joullié reaction, after 24 h, additional 0.2 equivalents of isocyanide were added. Chromatography was carried out with PE: AcOEt 2:1→1:1, affording a complete separation of the two diastereomers. The minor diastereomer **21k** was not isolated. An overall yield 71% was calculated on the basis of d.r. The d.r. was = 95: 5 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 50:50 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **20k**: 13.59. R_t of **21k**: 12.51. Minor diastereomer **21k** was recognized using a MS (ESI) detector. White solid. R_f = 0.30 (PE/AcOEt 2 : 1). R_f of **21k** = 0.42. $[\alpha]_D$ = −46.2 (c 1.0, $CHCl_3$). M.p.: 180.3-181.8 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.74 (d, J = 2.1 Hz, Ar, 1H), 7.39 (dd, J = 8.7, 2.5 Hz, Ar, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.62 (broad s, N*H*, 1H), 5.62 (broad s, C*H*C=O, 1H), 4.85 (d, J = 13.0 Hz, C*H*HO, 1H), 4.45 (broad quintuplet, J = 5.9 Hz, C*H*CH_3, 1H), 4.18 (dd, J = 13.0, 4.9 Hz, C*H*HO, 1H), 2.12 (s, C*H*$_3$C=O, 3H), 1.25 (s, C(C*H*$_3$)$_3$, 9H), 1.10 (d, J = 6.9 Hz, C*H*$_3$CH, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C): δ 169.4, 168.6 (*C*=O), 154.9, 123.3, 111.6 (quat.), 134.3, 131.9, 120.7 (aromatic *C*H), 69.5 (*C*H_2O), 61.6 (broad) (*C*HC=O), 51.4 (broad) (*C*HN), 50.3 (*C*NH), 27.8 (C(*C*H_3)$_3$, 21.1 (*C*H_3=O), 16.2 (*C*H_3CH). I.R. (ATR): ν_{max} 3413, 3336, 2969, 2930, 1685, 1630, 1570, 1514, 1487, 1449, 1418, 1389, 1369, 1335, 1319, 1299, 1281, 1267, 1254, 1221, 1179, 1146, 1125, 1106, 1090, 1066, 1042, 1000, 962, 929, 903, 877, 823, 766, 740, 709, 689, 659, 624 cm^{-1}.HRMS (ESI+): found 383.0974 [Calcd for $C_{17}H_{24}BrN_2O_3^+$ (M + H)$^+$ 383.0970].

Synthesis of (*3R,5S*)-4-(3-Acetyl)-7-bromo-*N*-(*tert*-butyl)-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (*ent*-20k).

It was prepared exactly as for the enantiomer **20k**. $[\alpha]_D$ = +44.9 (c 1.0, $CHCl_3$). All the other data were identical to those of the enantiomer.

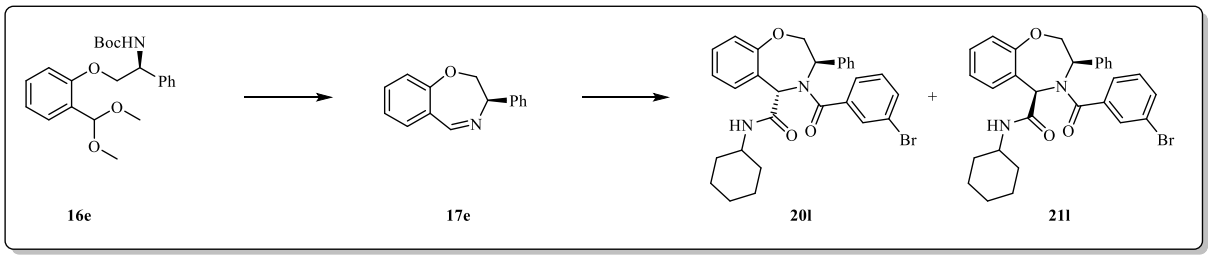
Synthesis of (*3S,5R*)-7-Bromo-4-(5-chlorothiophene-2-carbonyl)-*N*-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20i).



Acetal **16d** (395.4 mg, 976 µmol) was dissolved in CH_2Cl_2 (3.7 mL) and treated with 37% aqueous HCl (808 µL, 9.67 mmol). The mixture was stirred at rt for 5 h. Then it was diluted with CH_2Cl_2, and cautiously treated with a solution of Na_2CO_3 (765 mg, 7.21 mmol) in water (16.0 mL). After checking that pH > 9, the two phases were separated, washed with brine, and evaporated to dryness. The resulting crude imine **17d** (yellow oil)(197.5 mg) was taken up in dry methanol (4.75 mL), and treated with *tert*-butyl isocyanide (131 µl, 1.15 mmol) and with 3-((tert-butyldimethylsilyl)oxy)propanoic acid (252 mg, 1.15 mmol). The mixture was stirred at rt for 24 h. Then further *tert*-butyl isocyanide (21 µL, 0.25 mmol) were added. After strring for 24 h more, the mixture was evaporated to dryness and chromatographed (PE: AcOEt 5:1) to give pure **20i** (284 mg, 54%). The minor diastereome **21i** was not isolated. The ratio **20i**:

21i was determined by HPLC on the crude product and resulted = 95:5. HPLC conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 50:50 + 1% CF_3CO_2H up to 20 minutes. Then 100% MeOH + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **20i**: 20.82. R_t of **21i**: 20.45. Minor diastereomer **20i** was recognized using a MS (ESI) detector. The overall yield was calculated to be 57% on the basis of d.r. Oil. R_f = 0.33 (PE: AcOEt 5: 1). $[\alpha]_D$ = −23.0 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.72 (d, J = 2.5 Hz, Ar, 1H), 7.39 (dd, J = 8.7, 2.5 Hz, 1H), 6.85 (d, J = 8.7 Hz, 1H), 6.57 (broad s, N*H*, 1H), 5.64 (broad s, C*H*C=O, 1H), 4.82 (d, J = 13.1 Hz, C*H*HO, 1H), 4.47 (broad quintuplet, J = 6.1 Hz, C*H*CH_3, 1H), 4.18 (dd, J = 13.1, 4.9 Hz, C*H*HO, 1H), 3.64 (t, J = 6.4 Hz, C*H*$_2$OSi, 2H), 2.55 (dt, J = 15.6, 7.2 Hz, C*H*HC=O, 1H), 2.37 (dt, J = 15.6, 7.2 Hz, C*H*HC=O, 1H), 1.77 (quintuplet, J = 6.9 Hz, C*H*$_2$CH$_2$OSi, 2H), 1.25 (s, C(C*H*$_3$)$_3$, 9H), 1.11 (d, J = 6.8 Hz, C*H*$_3$CH, 3H), 0.89 (s, SiC(C*H*$_3$)$_3$, 9H), 0.05 (s, (C*H*$_3$)$_2$Si, 6H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 171.7, 168.6 (*C*=O), 155.0, 123.4, 111.6 (quat.), 134.2, 131.9, 120.6 (aromatic *C*H), 69.4 (*C*H$_2$O), 61.4 (*C*H$_2$OSi), 61.2 (broad) (*C*HC=O), 51.1 (*C*HN), 50.2 (*C*NH), 28.4 (*C*H$_2$C=O), 27.8 (C(*C*H$_3$)$_3$, *C*H$_2$CH$_2$OSi), 25.3 (SiC(*C*H$_3$)$_3$), 17.3 (Si*C*(CH$_3$)$_3$)), 16.2 (*C*H$_3$CH), −5.9 ((*C*H$_3$)$_2$Si). I.R. (ATR): ν_{max} 3418, 3344, 2956, 2929, 2857, 1686, 1625, 1538, 1507, 1486, 1472, 1462, 1454, 1412, 1393, 1365, 1323, 1273, 1250, 1235, 1181, 1124, 1100, 1060, 1005, 968, 939, 834, 775, 752, 679, 664, 626, 612 cm^{-1}.HRMS (ESI+): found 541.2103 [Calcd for $C_{25}H_{42}BrN_2O_4Si^+$ $(M + H)^+$ 541.2097].

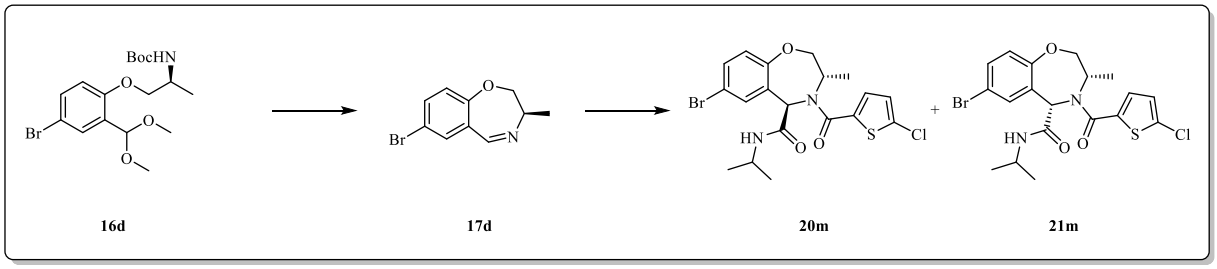
Synthesis of (*3R,5S*)-4-(3-Bromobenzoyl)-*N*-(cyclohexyl)-3-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20l).



It was prepared in 86% yield from (*R*)-**16e**, 3-bromoacetic acid and cyclohexyl isocyanide, following the typical procedure described for **20b**. However, in this case, 1.3 equivalents of isocyanide were used. Chromatography was carried out with PE: AcOEt 3:1→AcOEt: MeOH 95:5, affording a complete separation of the two diastereomers. The minor diastereomer **21l** was not isolated. An overall yield 89% was calculated on the basis of d.r. The d.r. was = 97: 3 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 30:70 + 1% TFA. Detection: UV 220 nm. R_t of **20l**: 10.93. R_t of **21l**: 11.72. Minor diastereomer **21l** was recognized using a MS (ESI) detector. White solid. R_f = 0.36 (PE: AcOEt 3: 1). $[\alpha]_D$ = −98.5 (c 1.0, $CHCl_3$). M.p: 229.0-231.5 °C. ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.61 (d, J = 7.8 Hz, Ar, 1H), 7.41-7.22 (m, Ar, 4H), 7.21-7.05 (m, Ar, 6H), 6.95 (td, J = 7.4, 0.9 Hz, Ar, 1H), 6.71 (d, J = 8.1, Ar, 1H), 6.65 (broad d, J = 6.6 Hz, N*H*, 1 H), 5.78 (broad s, C*H*C=O, 1H), 5.44 (broad s, C*H*Ph, 1H), 5.03 (dd, J = 13.6, 1.4 Hz, C*H*HO, 1H), 4.53 (dd, J = 13.6, 4.0 Hz, C*H*HO, 1H), 3.70-3.55 (broad m, C*H*NH, 1H), 1.82-1.47 (m, C*H*$_2$ cyclohexyl, 5H), 1.40-1.05 (m, C*H*$_2$ cyclohexyl, 5H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 169.7, 168.5 (*C*=O), 155.3, 138.8, 138.1, 121.0, 120.3 (quat.), 132.1, 131.8, 130.0, 129.4, 128.4, 127.2 (x2), 125.9, 125.6 (x2), 124.6, 120.9, 118.9 (aromatic *C*H), 68.5 (*C*H$_2$O), 64.1 (broad) (*C*HC=O), 60.5 (broad) (*C*HN), 48.1

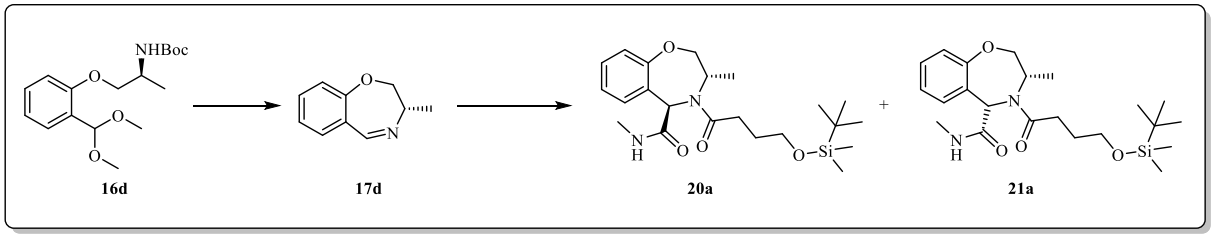
(*C*HNH), 31.1 (x2), 24.5, 23.8, 23.7 (*C*H_2 cyclohexyl). I.R. (ATR): ν_{max} 3320, 3063, 3028, 2924, 2850, 1663, 1650, 1610, 1581, 1563, 1512, 1490, 1464, 1449, 1414, 1389, 1352, 1332, 1311, 1275, 1249, 1219, 1178, 1148, 1115, 1080, 1046, 1027, 998, 977, 956, 917, 903, 894, 879, 866, 854, 823, 798, 777, 753, 741, 731, 691, 647 cm^{-1}. HRMS (ESI+): found 533.1429 [Calcd for $C_{29}H_{30}BrN_2O_3^+$ $(M + H)^+$ 533.1440].

Synthesis of (*3S*,*5R*)-7-Bromo-4-(5-chlorothiophene-2-carbonyl)-*N*-isopropyl-3-methyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine-5-carboxamide (20m).



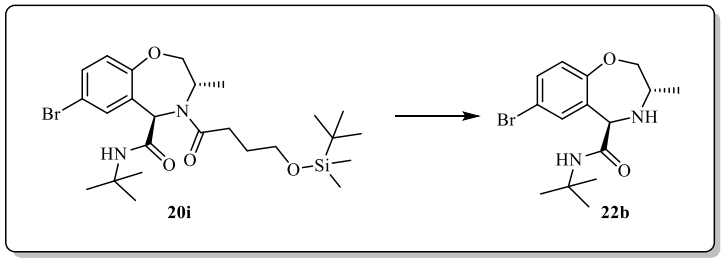
It was prepared in 60% yield from (*S*)-**16d**, 5-chloro-2-thienoic acid and isopropyl isocyanide, following the typical procedure described for **20b**. However, in this case, for the Ugi-Joullié reaction, 1.4 equivalents of isocyanide were used. Chromatography was carried out with PE: AcOEt 4:1→3:1. The minor diastereomer **21m** was not isolated. The overall yield was calculated to be 63% on the basis of d.r. The d.r. was = 95: 5 by HPLC of the crude product. Conditions: column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 50:50. Detection: UV 220 nm. R_t of **20m**: 16.27. R_t of **21m**: 15.68. Minor diastereomer **21m** was recognized using a MS (ESI) detector. White solid. R_f = 0.33 (PE: AcOEt 4: 1). $[\alpha]_D$ = −71.3 (c 1.0, $CHCl_3$). M.p.: 166.8-169.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 20 °C) δ 7.41 (dd, J = 8.7, 2.4 Hz, Ar, 1H), 7.22 (d, J = 2.3 Hz, Ar, 1H), 7.17 (d, J = 3.9 Hz, Ar, 1H), 6.90-6.85 (m, Ar, 2H), 5.63 (broad s, C*H*C=O, 1H), 5.49 (broad s, N*H*, 1H), 4.63 (d, J = 13.5 Hz, C*H*HO, 1H), 4.70-4.58 (m, C*H*CH_3, 1H), 1.31 (d, J = 6.8 Hz, CH_3CH, 3H), 1.12 (d, J = 6.6 Hz, C$H_3$$CHCH_3$, 3H), 1.10 (d, J = 6.6 Hz, C$H_3$$CHCH_3$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 20 °C) δ 168.8, 164.6 (*C*=O), 155.5, 135.7, 134.6, 122.1, 113.7 (quat.), 134.1, 133.8, 128.6, 126.2, 121.9 (aromatic *C*H), 70.2 (*C*H_2O), 64.4 (*C*HC=O), 53.9 (*C*HN), 42.5 (*C*HNH), 22.4, 22.3 (*C*H_3)$_2$CH, 16.8 (*C*H_3CH). I.R. (ATR): ν_{max} 3283, 3094, 2977, 2933, 2876, 1657, 1623, 1514, 1486, 1434, 1386, 1344, 1316, 1277, 1251, 1220, 1186, 1145, 1129, 1107, 1059, 998, 951, 933, 874, 859, 840, 771, 743, 688 cm^{-1}.HRMS (ESI+): found 471.0156 [Calcd for $C_{19}H_{21}BrClN_2O_3S^+$ $(M + H)^+$ 471.0145].

Synthesis of (3S,5R)-4-(4-((tert-butyldimethylsilyl)oxy)butanoyl)-N,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (20a)



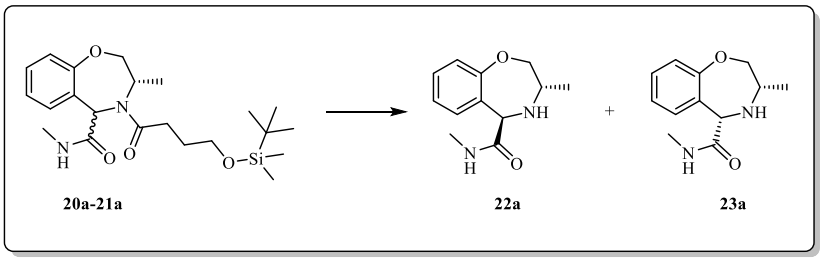
Acetal **16d** (1.3681 g, 4.20 mmol) was dissolved in CH_2Cl_2 (15 mL) and treated with 37% aqueous HCl (3.48 mL, 41.7 mmol). The mixture was stirred at rt for 5 h. Then it was diluted with CH_2Cl_2, and cautiously treated with a solution of Na_2CO_3 (3.793 g, 35.7 mmol) in water (65 mL). After checking that pH > 9, the two phases were separated, washed with brine, and evaporated to dryness. The resulting crude imine **17d** (yellow oil)(611.1 mg) was taken up in dry methanol (21.0 mL), and treated with methyl isocyanide (300 µl, 5.04 mmol) and with 3-((tert-butyldimethylsilyl)oxy)propanoic acid (1.2836 g, 5.88 mmol). The mixture was stirred at rt for 24 h. Then further methyl isocyanide (100 µL, 1.68 mmol) was added. After stirring for 24 h more, the reaction mixture was heated up to 40°C. After 24h it was evaporated to dryness and chromatographed (PE: AcOEt 1:1) to give the final product (1.0886 g, 62%) as a mixture of diastereoisomers not separable. The ratio **20a**: **21a** was determined by HPLC both on the crude and pure product and resulted = 96:4. HPLC conditions: column DAICEL CHIRAL PAK AD 0.46 cm x 25cm. Flow: 0.8 ml/min. Temp: 25°C. Eluent: Exan: *i*PrOH 90:10. Detection: UV 220 nm. Rt of **20a**: 10.0. Rt of **21a**: 8.7. R_f = 0.25 (PE/AcOEt 1:1). $[\alpha]_D$ = −66.4 (c 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, DMSO-d_6, 90 °C) δ 7.41-7.28 (m, Ar, 1H), 7.27-7.25 (m, Ar, 1H), 7.10 (br, NH, 1H), 6.95-6.85 (m, Ar, 2H), 5.67 (s, CO*CH*N, 1H), 4.77 (d, J= 12.9 Hz, OC*H*H, 1H), 4.46 (bs, *CH*CH_3, 1H), 4.14 (dd, J=, 13.21, 4.01 Hz, OC*H*H, 1H), 3.64 (t, J= 6.39 Hz, COC*H*H, 1H), 3.46 (t, J= 6.28, COC*H*H, 1H), 2.62 (d, J= 4.50 Hz, NH*CH$_3$*, 3H), 2.57-2.55 (m, SiOC*H*H, 1H), 2.40-2.36 (m, SiOC*H*H, 1H), 1.81-1.72 (m, $COCH_2$*CH$_2$*, 2H), 1.08 (d, J= 6.79 Hz, CH*CH$_3$*, 3H), 0.87 (s, ^{t}Butyl, 9H), 0.04 (s, Si*CH$_3$*, 3H), -0.01 (Si*CH$_3$*, 3H). ^{13}C NMR (75 MHz, DMSO-d_6, 90 °C) δ 172.8, 172.4, 171.3, 156.3 (quat.), 133.7, 130.3, 121.5, 119.3 (aromatic CH), 69.9 (O*CH$_2$*), 62.4 (CO*CH$_2$*), 60.8 (CO*CH$_2$*), 52.1 (*CH*CH_3), 30.0 (SiOC*H$_2$*), 28.9 ($COCH_2$*CH$_2$*), 26.7 (NH*CH$_3$*), 26.2 (^{t}Butyl), 17.5 (CH*CH$_3$*), -2.8 (Si*CH$_3$*), -4.86 (Si*CH$_3$*). I.R. (ATR): ν_{max}: 2435, 3345, 2955, 2930, 2857, 1669, 1634, 1520, 1492, 1409, 1278, 1249, 1222, 1100, 1067, 966, 834, 750, 663.

Typical procedure for the synthesis of *trans*-secondary amines: (3*S*,5*R*)-7-Bromo-N-(*tert*-butyl)-3-methyl-2,3,4,5tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (22b).



Compound **20i** (75.2 mg, 139 mmol) was dissolved in a 1.0 M solution of camphorsulfonic acid in dry MeOH (0.60 mL), and stirred overnight at 40 °C. Then it was diluted with AcOEt and washed with a 1: 1 mixture of saturated aqueous $NaHCO_3$ and brine. The final pH of aqueous phase was 8. The phases were separated, and the organic one evaporated to dryness and chromatographed (PE: AcOEt 2: 1 + 1% EtOH up to PE: AcOEt 1: 1 + 1% EtOH) to give pure **22b** as a white solid (29 mg, 62%). R_f = 0.55 (PE: AcOEt 2: 1). $[a]_D$ = +28.6 (c 0.6, $CHCl_3$). Mp: 154.0– 156.2°C. ^{1}H NMR (300MHz,CDCl3,20°C): δ 7.34(dd,J= 8.4,2.4Hz, Ar, 1H), 7.29 (d,J= 2.4Hz, Ar, 1H), 6.92 (d, J= 8.4Hz, Ar, 1H), 5.96 (broad s, N*H*, 1H), 4.40 (s, C*H*C=O, 1H), 4.12 (dd, J= 11.6, 2.0 Hz, C*H*HO, 1H), 3.50–3.31 (m, C*H*HO, C*H*N, 2H), 1.32 (s, $C(CH_3)_3$, 9H), 1.07 (d, J = 6.3 Hz, CH_3CH, 3H,). ^{13}C NMR (75 MHz, $CDCl_3$, 25°C): δ 169.3 (C=O), 157.7, 133.7, 116.2 (quat.), 133.6, 132.3, 123.4 (aromatic CH), 78.4 (CH_2O), 64.3 (CHC=O), 51.5 (CNH), 50.8 (CHN), 28.7 ($C(CH_3)_3$), 17.8 (CH_3CH). IR (ATR): ν_{max} 3320, 3295, 2995, 2970, 2930, 2869, 1745, 1673, 1520, 1502, 1483, 1452, 1391, 1363, 1345, 1298, 1268, 1243, 1222, 1194, 1166, 1114, 1080, 1045, 1016, 985, 941, 928, 907, 874, 819, 786, 761, 726, 661 cm^{-1}. HRMS (ESI$^+$): found 341.0870 [calcd for $C_{15}H_{22}BrN_2O_2^+$ $(M + H)^+$ 341.0865].

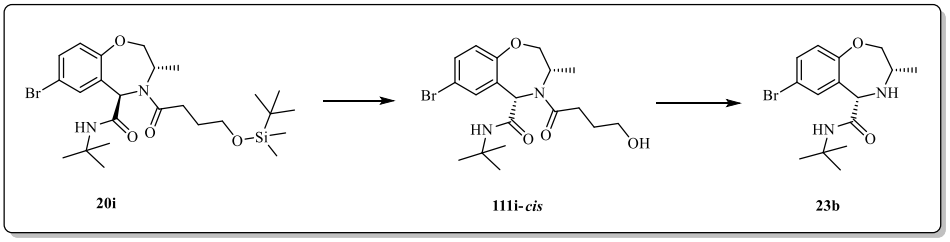
Synthesis of (3S,5R)-N,3-dimethyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (22a).



It was prepared from **20a-21a** following the typical procedure described for **22a**. The substrate was used as a mixture of diastereomers. Chromatography was carried out with PE: AcOEt 1:2 and 5% of MeOH. Separation of the two diastereomers was not complete. We obtained fractions with pure **22a** plus some fractions contaminated with little **23a**. The overall yield was 58%. R_f **22a** = 0.21 (PE: AcOEt 1:2 and 5% of MeOH). $[\alpha]_D$ = +13.2 (c 1.0, $CHCl_3$). Mp: 154.9– 155.5°C. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.31-7.25 (m, Ar, 1H), 7.21-7.20 (m, Ar, 1H), 7.18-7.05 (m, Ar, 2H), 5.72 (bs, NH, 1H), 4.49 (s, CO*CH*, 1H), 4.12 (d, J= 9.76 Hz, OC*H*H, 1H), 3.50-3.39 (m, OC*H*H, *CH*CH_3, 2H), 2.77 (d, J= 4.87 Hz, NHCH_3, 3H), 1.06 (d, J= 6.19 Hz, CHCH_3, 3H).^{13}C NMR (75 MHz, Chloroform-d) δ 171.9, 158.6 (quat.), 131.4, 131.1, 129.9, 124.2, 122.1 (aromatic CH), 78.6 (OCH_2), 65.1 (CO*CH*), 51.2 (*CH*CH_3), 26.5 (NHCH_3), 18.0 (CHCH_3). I.R. (ATR): ν_{max}: 3673, 3310, 2973, 2939,

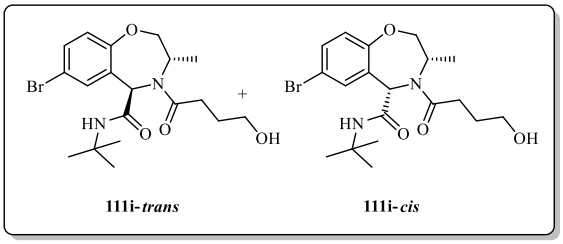
2867, 1651, 1583, 1520, 1485, 1461, 1444, 1407, 1388, 1364, 1345, 1279, 1252, 1207, 1168, 1120, 1032, 1005, 968, 945, 916, 885, 839, 804, 781, 754, 637, 616.

Typical procedure for the synthesis of *cis*-secondary amines: (3*S*,5*S*)-7-Bromo-N-(*tert*-butyl)-3-methyl-2,3,4,5tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (23b).



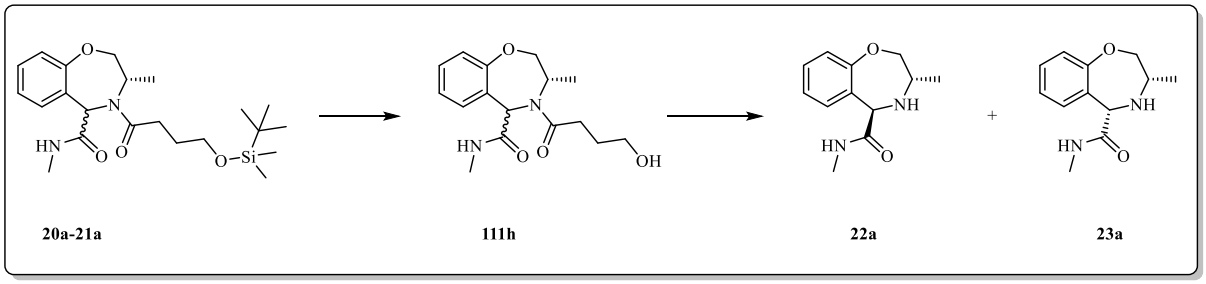
Compound **20i** (103.7 mg, 191 mmol) was dissolved in dry THF (1.22 mL) and treated with a 1M solution of tetrabutylammonium fluoride (TBAF) in THF (230 mL, 230 mmol). The mixture was stirred at rt for 2 h. Then it was diluted with AcOEt and washed with a 1: 1 mixture of brine and water. The organic phases were evaporated. HPLC analysis of this crude product indicated a d.r. of 90: 10 (see below for details). This crude product was chromatographed (PE/AcOEt 1: 2 + 1% EtOH) to give pure *cis* compound **111i** as a colorless oil (58mg, 71%). The overall yield, calculated from d.r., was 79%. This intermediate was dissolved in a 1M solution of camphor sulfonic acid in dry MeOH (0.63 mL), and stirred overnight at 40 °C. Then it was diluted with AcOEt and washed with a 1: 1 mixture of saturated aqueous $NaHCO_3$ and brine. The final pH of aqueous phase was 8. The phases were separated, and the organic one evaporated to dryness and chromatographed (PE: AcOEt 2: 1 + 1% EtOH up to PE: AcOEt 1 : 1 + 1% EtOH) to give pure **23b** as a white solid (36 mg, 77%). R_f = 0.55 (PE: AcOEt 2 : 1). $[a]_D$ = -57.0 (c 1.0, $CHCl_3$). Mp: 107.6– 110.0 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) δ 7.39 (d, J= 2.4 Hz, Ar, 1H), 7.30 (dd, J= 8.4, 2.4 Hz, Ar, 1H,), 7.10 (broad s, N*H*, 1H), 6.90 (d, J= 8.4 Hz, Ar, 1H), 4.53(s, C*H*C=O, 1H), 4.24 (d, J= 9.0 Hz, C*H*HO, 1H), 3.32–3.18 (m, C*H*HO, C*H*N, 2H), 1.43 (s, $C(CH_3)_3$, 9H), 1.03 (d, J= 5.6 Hz, CH_3CH, 3H). ^{13}C NMR (75 MHz, CDCl3, 25°C): δ 169.6 (C=O), 158.0, 137.0, 116.8 (quat.), 131.6, 130.4, 123.3 (aromatic CH), 78.6 (CH_2O), 61.4 (CHC=O), 54.5 (CHNH), 51.1 (CNH), 28.8 ($C(CH_3)_3$), 17.7 (CH_3CH). IR (ATR): ν_{max} 3338, 3286, 2965, 2931, 2875, 1661, 1513, 1477, 1457, 1392, 1365, 1316, 1300, 1286, 1264, 1245, 1223, 1164, 1144, 1104, 1085, 1047, 1009, 994, 939, 915, 903, 884, 874, 852, 829, 823, 805, 774, 751, 730, 675, 623cm^{-1}. HRMS (ESI$^+$): found 341.0866 [calcd for $C_{15}H_{22}BrN_2O_2^+$ $(M + H)^+$ 341.0865].

HPLC conditions for analysis of the diastereomeric ratio of 111i-*cis* and 111i-*trans*.



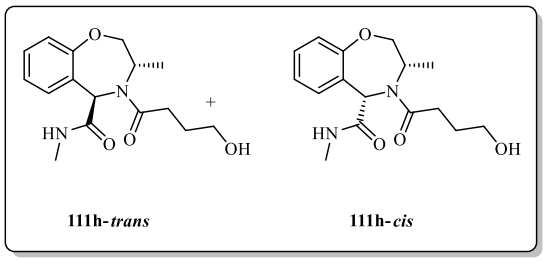
Column Luna C8 150 x 4.6 mm, 5 µ. Flow: 0.8 ml/min. Temp: 25°C. Eluent: H_2O: MeOH 90:10 + 1% CF_3CO_2H up to 20 minutes. Then 100% MeOH + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **111i-*trans***: 17.93. R_t of **111i-*cis***: 18.58. The ratio was 90: 10 (**111i-*cis***: **111i-*trans***).

Synthesis of (3S,5S)-N-(tert-butyl)-3-methyl-2,3,4,5-tetrahydrobenzo[f][1,4]oxazepine-5-carboxamide (23a).



It was prepared from **20a-21a** following the typical procedure described for **23b**. The substrate was used as a mixture of diastereomers. HPLC analysis of the crude product (**111h-*cis***: **111h-*trans***) indicated a d.r. of 73: 27 (see below for details). This crude product was used without any further purification in the final step. Separation of the two diastereomers was not complete. We obtained fractions with pure **23a** plus some fractions contaminated with little **22a**. The overall yield (calculated from **22a-23a**) was 77%. R_f **23a** = 0.26 (PE/AcOEt 1:2 and 5% of MeOH), $[\alpha]_D$ = -1.39 (c 1.0, $CHCl_3$). Mp: 164.9– 166.3°C. ^{1}H NMR (300 MHz, Chloroform-d) δ 7.38 (s, bs, N*H*, 1H), 7.27-7.18 (m, Ar, 2H), 7.07-7.02 (m, Ar, 2H), 4.72 (s, CO*CH*, 1H), 4.31-4.22 (m, OC*H*H, 1H), 3.34-3.14 (m, OC*H*H, *CH*CH_3, 2H), 2.91 (d, J= 4.96 Hz, NH*CH_3*, 3H), 1.03 (d, J= 6.08 Hz, CH*CH_3*, 3H). ^{13}C NMR (75 MHz, CDCl3, 25°C) δ 171.8 (C=O), 159.0, 134.8 (quat.), 129.0, 127.3, 124.3, 121.7 (aromatic CH), 78.8 (CH_2O), 61.6 (CHC=O), 55.0 (CHNH), 26.1 ($NHCH_3$), 17.8 (CH_3CH). I.R. (ATR): ν_{max}: 3368, 3264, 2966, 2894, 2858, 1649, 1598, 1576, 1537, 1481, 1455, 1410, 1381, 1315, 1268, 1216, 1173, 1143, 1117, 1088, 1038, 1008, 941, 893, 848, 800, 776, 752, 732, 661, 626.

HPLC conditions for analysis of the diastereomeric ratio of 111h-*cis* and 111h-*trans*.



Phenylic column C6 150 x 3 mm, 3µ. Flow: 0.34 ml/min. Temp: 25°C. Eluent: H_2O: MeCN 90:10 + 1% CF_3CO_2H up to 20 minutes. Then H_2O: MeCN 40: 60 + 1% CF_3CO_2H. Detection: UV 220 nm. R_t of **111h-*trans***: 12.08 R_t of **111h-*cis***: 11.12. The ratio was 73:27 (**111h-*cis***: **111h-*trans***).

Synthesis of 4-((*tert*-Butyldimethylsilyl)oxy)butanoic acid (109).

γ-Butyrolactone (1.526 mL, 20.0 mmol) was dissolved in a solution of NaOH (901.2 mg, 22.5 mmol) in MeOH (20.0 mL). The mixture was stirred at room temperature for 2 h. It was then evaporated and the crude product (2.7560 g) was taken up in dry DMF (40.0 mL). The mixture was cooled to 0°C and then *tert*-butyldimethylchlorosilane (6.5958 g, 43.8 mmol) and imidazole (4.5185 g, 66.3 mmol) were added. The mixture was stirred overnight at room temperature. It was diluted with PE / Et_2O 1:1 and washed with water. The organic phases were dried over Na_2SO_4, filtered and evaporated under reduced pressure at low temperature (the rotavapor bath was kept near 0°C). The resulting colourless oil (9.1058 g) was taken up

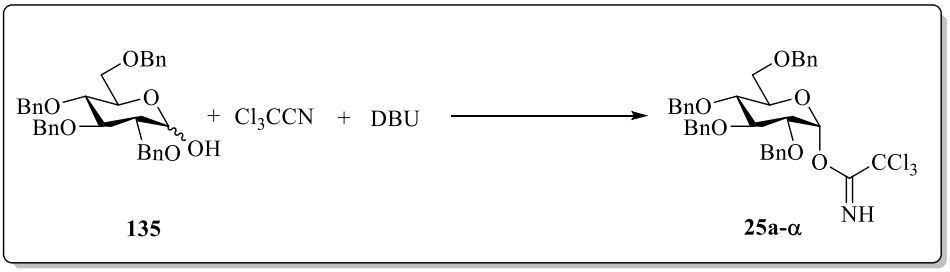
with a mixture of water (60.0 mL), MeOH (20.0 mL), THF (20.0 mL), and treated with K_2CO_3 (5.5382 g, 40.0 mmol). The resulting mixture was stirred at room temperature overnight. It was then concentrated to remove most MeOH and THF, diluted with Et_2O and extracted with water. The aqueous phase was acidified to pH = 2 with HCl 1M and extracted with Et_2O. The organic phases were dries over Na_2SO_4, filtered and evaporated under reduced pressure. The desired product (3.7923 g, 87%) was obtained as a colorless oil and used as such without any purification.

3.5 N- vs. O-Glycosylation

General experimental details

All chemicals used have been used in synthesis purchased at Sigma-Adrich, Fluka, TCI, ABCR, CarboSynth or Merck unless otherwise noted. All solvents used for synthesis were HPLC-grade and obtained dry from an Innovative Technology PS-MD-05 solvent drying system. ROTH silica gel 60 (40-63 mesh) has been used as stationary phase for column chromatography. Merck 60 F254-plates were used for TLC-analysis, visualized by UV and submerged in Ce/Mo-solution (Ce(IV)sulphate (10 g) and $(NH_4)_2MO_4$ (15 g) in 1000 mL 10 % aqueoussulphuric acid), 10 % H_2SO_4 in methanol or vanillin stain (10 g, in 1000 mL 10 % H_2SO_4 in MeOH) followed by heating. All reactions were carried out under an inert nitrogen atmosphere in flame-dried glassware unless otherwise stated. A Bruker 500 MHz Ultra Shield Plus spectrograph with a cryo probe has been used to obtain ^{1}HNMR-, ^{13}C-NMR-, COSY- (Correlation Spectroscopy) and HSQC-spectra (Heteronuclear Single Quantum Coherence). High-resolution mass spectrometry has been performed on a Bruker SolarX XR 7T E8I/MALDI-FTICR-MS instrument.

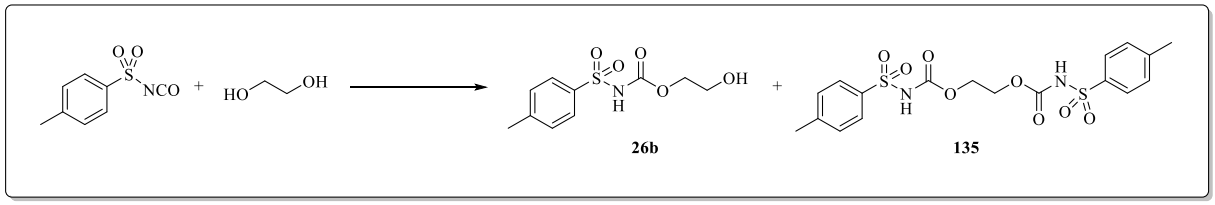
Synthesis of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (25a-α)



135 25a-α

Trichloroacetonitrile (4.00 mL, 39.9 mmol) was added to a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (4.0 g, 7.43 mmol) in dry DCM (40 mL). Then, DBU (115 µL, 0.768 mmol) was added slowly. The solution was stirred overnight at RT. Et_3N (5.5 mL, 39.9 mmol) was added and the solution was stirred for 10 minutes at RT. The solvent was evaporated under reduced pressure and the crude product was purified through chromatographic column (EPT: AcOEt 3:1) to yield the desired product (4.34 g, 6.3 mmol, 85%) as a yellow oil. NMR is in accordance with the literature.[15] α-anomer: ^{1}H NMR (500 MHz, Chloroform-d) δ 8.58 (s, NH, 1H), 7.37-7.25 (m, Ar, 18H), 7.19-7.14 (m, Ar, 2H), 6.53 (d, J=3.6 Hz, H-1, 1H), 4.96 (d, J=10.9 Hz, CH_2,1H), 4.86 (d, J=10.6 Hz, CH_2,1H), 4.83 (d, J=11.0 Hz, CH_2,1H), 4.75 (d, J=11.7 Hz, CH_2, 1H), 4.68 (d, J=11.7 Hz, CH_2,1H), 4.61 (d, J=12.0 Hz, CH_2, 1H), 4.53 (d, J=10.5 Hz, CH_2,1H), 4.47 (d, J=12.1 Hz, CH_2,1H), 4.06 (t, J=9.4 Hz, H-3, 1H), 3.99 (dt, J=2.56 Hz, J=10.1 Hz, H-5, 1H), 3.81-3.76 (m, H-2, H-4, H-6a, 3H), 3.67 (dd, J=2.0, J=11.0 Hz, H-6b, 1H) ppm.

Synthesis of 2-hydroxyethyl tosylcarbamate (26b) and **ethane-1,2-diyl bis(tosylcarbamate) (135)**

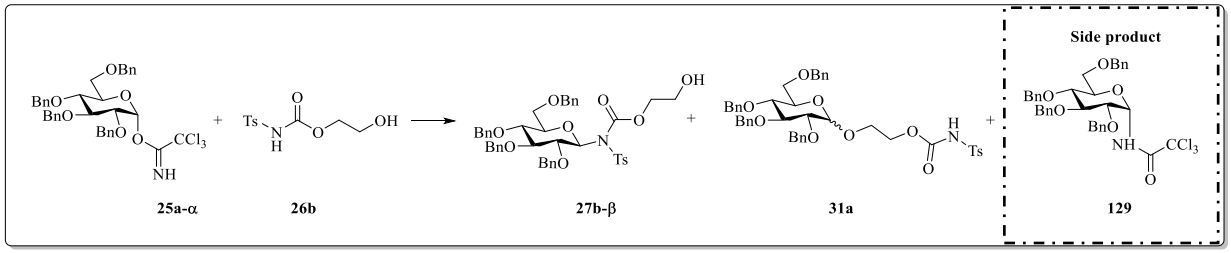


Tosyl isocyanate (2.3 mL, 15.1 mmol) was added slowly to a flask, in an ice bath, containing a solution of ethylene glycol (4.2 mL, 75.1 mmol) in acetone (127 mL). The reaction mixture was allowed to warm up to RT and stirred overnight. The solvent was removed under reduced pressure and the crude product was purified through chromatographic column with the eluent DCM: AcOEt 4:1 + 1% of HCOOH to yield **135** as a white solid (R_f = 0.43, 1.0 g, 2.2 mmol, 15%) up to + 1% of HCOOH up to 1:1 + 1% of HCOOH to yield **26b** as a white solid (R_f = 0.45, 2.2 g, 8.5 mmol, 56%).

2-hydroxyethyl tosylcarbamate (26b): The desired product was recrystallized with AcOEt. ^{1}H NMR (500 MHz, Acetone-d6) δ 10.3 (s, NH, 1H), 7.92-7.89 (m, Ar, 2H), 7.44-7.43 (m, Ar, 2H), 4.10-4.08 (m, CH_2, 2H), 3.66 (t, J= 4.96, CH_2,2H), 2.44(s, CH_3, 3H) ppm. ^{13}C NMR (126 MHz, Acetone-d6) δ 151.9 (C=O), 145.4 (iC^{Ts}), 137.7 (iC^{Ts}), 130.3 (m-CH, 2C), 128.9 (o-CH, 2C), 68.6 (CH_2), 60.5 (CH_2), 21.5 (CH_3). HRMS (MALDI+): Calculated for $C_{10}H_{13}NO_5SNa^+$ m/z 282.04066; found m/z 282.04060. m.p.= 130-133 °C.

Ethane-1,2-diyl bis(tosylcarbamate) (135): The product was recrystallized with MeOH. ^{1}H NMR (500 MHz, Acetone-d6) δ 10.4 (s, NH, 2H), 7.92-7.88 (m, Ar, 4H), 7.44-7.42 (m, Ar, 4H), 4.19 (s, CH_2, 4H), 2.45-2.44 (m, CH_3, 6H). ^{13}C NMR (126 MHz, Acetone-d6) δ 151.5 (C=O), 145.6 (iC^{Ts}), 137.6 (iC^{Ts}), 130.4 (m-CH, 2C), 128.9 (o-CH, 2C), 64.5 (CH_2, 4C), 21.5 (CH_3, 2C). HRMS (MALDI+): Calculated for $C_{18}H_{20}N_2O_8S_2Na^+$ m/z 479.05533; found m/z 479.05215. m.p.= 205-208 °C.

PROCEDURES AND RESULTS FOR N- and O-GLYCOSYLATION REACTIONS



Procedure A: 2-hydroxyethyl tosylcarbamate (57 mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (2 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure. The crude product (colorless oil, 160 mg) was purified through chromatographic column (EPT: AcOEt 2:1).

Procedure B: 2-hydroxyethyl tosylcarbamate (57 mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100

mg, 0.146 mmol) in dry solvent (2 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure without any purifications of the crude product (colorless oil, 160 mg).

Procedure C: 2-hydroxyethyl tosylcarbamate (25.7 mg, 0.099 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (2,00 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure without any purifications of the crude product.

Procedure D: 2-hydroxyethyl tosylcarbamate (57 mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (1 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure without any purifications of the crude product.

Procedure E: 2-hydroxyethyl tosylcarbamate (57 mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (10 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure without any purifications of the crude product.

Procedure F: 2-hydroxyethyl tosylcarbamate (7.6 mg, 0.0293 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (2,00 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure without any purifications of the crude product.

Procedure G: 2-hydroxyethyl tosylcarbamate (191 mg, 0.735 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (2 mL). The reaction mixture was stirred for 48h. The reaction mixture was extracted with NaOH 1M, to remove the excess of carbamate, washed with NH_4Cl, Brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 90 mg of crude product as yellow oil.

Procedure H: 2-hydroxyethyl tosylcarbamate (47 mg, 0.181 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry solvent (2 mL). The reaction mixture was stirred for 48h. The solvent was removed under reduced pressure. The crude product (yellow oil, 160 mg) was purified through chromatographic column (EPT: AcOEt 2:1).

Procedure I: 2-hydroxyethyl tosylcarbamate (57mg, 0,220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) and TfOLi (4 mg, 20% mol) in dry solvent (2mL). The reaction mixture was stirred for 48h. Then, it was extracted with NaOH 1M, washed with NH_4Cl, Brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 90 mg of crude product as yellow oil.

Procedure J: 2-hydroxyethyl tosylcarbamate (57mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) and Tf_2NLi (8 mg, 20% mol) in dry solvent (2 mL). The reaction mixture was stirred for 48h. Then, it was extracted with NaOH 1M, washed with NH_4Cl, Brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain 99 mg of crude product as yellow oil.

TABLE A: Increase of solvent's polarity

Procedure	*α-Trichloroacetimidate (1)*	*2-hydroxyethyl tosylcarbamate*	*Solvent*	*T (°C)*	*N-Glycosylation: O-Glycosylation***	*α: β (5)**	*Yield (%) 27b-β*	*Yield (%) 31a*	*43***
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	Toluene	40	87:13	1:1	/	/	/
A	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	46:54	1:1	34	40	/
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	THF	RT	56:44	1:1	/	/	/
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	$MeNO_2$	RT	0:100	1:1	/	/	13%

*The data reported were estimated through $^{13}C(^{1}H)$-NMR. **The data reported were determined through ^{1}H-NMR of the crude product.

TABLE B: Increase of the carbamate's molarity

Procedure	*α-Trichloroacetimidate (1)*	*2-hydroxyethyl tosylcarbamate*	*Solvent*	*T (°C)*	*N-Glycosylation: O-Glycosylation***	*α: β (5)**	*Yield (%) 27b-β*	*Yield (%) 31a*	*43***
F	0.073 M (5.0 eq.)	0.0146 M (1.0 eq.)	Toluene	40	100:0	/	/	/	37%
C	0.073 M (1.5 eq.)	0.049 M (1.0 eq.)	Toluene	40	85:15	3:1	/	/	14%
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	Toluene	40	87:13	1:1	/	/	/
G	0.073M (1.0 eq.)	0.367 M (5.0 eq.)	Toluene	40	47:53	3:1	/	/	34%
F	0.073 M (5.0 eq.)	0.0146 M (1.0 eq.)	DCM	RT	70:30	3:1	/	/	30%
C	0.073 M (1.5 eq.)	0.049 M (1.0 eq.)	DCM	RT	70:30	1:2	/	/	/
H	0.073 M (1.0 eq.)	0.0905 M (1.2 eq.)	DCM	RT	60:40	1:3	/	/	/
A	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	46:54	1:1	34	40	/
G	0.073M (1.0 eq.)	0.367M (5.0 eq.)	DCM	RT	14:86	1:1	/	/	19%

*The data reported were estimated through $^{13}C(^{1}H)$-NMR. **The data reported were determined through ^{1}H-NMR of the crude product.

TABLE C: The use of different concentration

Procedure	*α-Trichloroacetimidate (1)*	*2-hydroxyethyl tosylcarbamate*	*Solvent*	*T (°C)*	*N-Glycosylation: O-Glycosylation***	*α: β (5)**	*Yield (%) 27b-β*	*Yield (%) 31a*	*43***
D	0.146 M (1.0 eq.)	0.220 M (1.5 eq.)	Toluene	40	83:17	3:1	/	/	7%
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	Toluene	40	87:13	1:1	/	/	/
E	0.0146 M (1.0 eq.)	0.022 M (1.5 eq.)	Toluene	40	75:25	1:1	/	/	/
D	0.146 M (1.0 eq.)	0.220 M (1.5 eq.)	DCM	RT	27:73	1:1	/	/	8%
A	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	46:54	1:1	34	40	/
E	0.0146 M (1.0 eq.)	0.022 M (1.5 eq.)	DCM	RT	56:44	1:3	/	/	/

*The data reported were estimated through $^{13}C(^{1}H)$-NMR. **The data reported were determined through ^{1}H-NMR of the crude product.

TABLE D: The use of Lithium salts

Procedure	*α-Trichloroacetimidate (1)*	*2-hydroxyethyl tosylcarbamate*	*Solvent*	*T (°C)*	*N-Glycosylation: O-Glycosylation***	*α: β (5)**	*Yield (%) 27b-β*	*Yield (%) 31a*	*43***
A	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	46:54	1:1	34	40	/
I	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	0:100	1:1	/	/	15%
J	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	DCM	RT	0:100	1:1	/	/	13%

*The data reported were estimated through $^{13}C(^{1}H)$-NMR. **The data reported were determined through ^{1}H-NMR of the crude product.

TABLE E: The use of different temperature in Toluene

Procedure	*α-Trichloroacetimidate (1)*	*2-hydroxyethyl tosylcarbamate*	*Solvent*	*T (°C)*	*N-Glycosylation: O-Glycosylation***	*α: β (5)**	*Yield (%) 27b-β*	*Yield (%) 31a*
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	Toluene	RT	83:17	1:1	/	/
B	0.073 M (1.0 eq.)	0.110 M (1.5 eq.)	Toluene	40	87:13	1:1	/	/

*The data reported were estimated through $^{13}C(^{1}H)$-NMR. **The data reported were determined through ^{1}H-NMR of the crude product.

2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl 2-hydroxyethyl tosylcarbamate (27b-β)

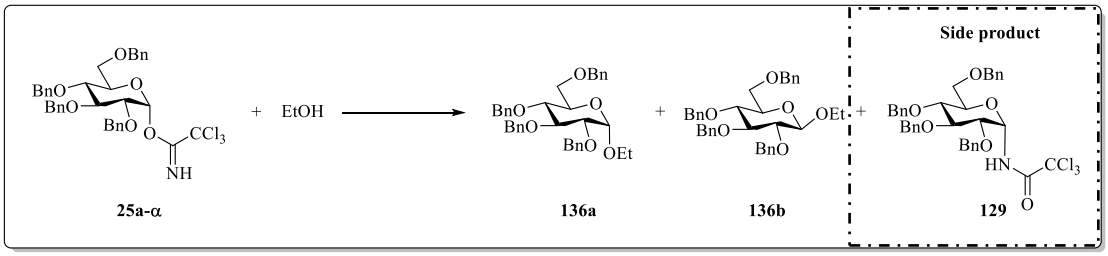
The product was isolated as a colorless oil (R_f = 0,37, PE:AcOEt 1:1+2% of MeOH) . ^{1}H NMR (500 MHz, Chloroform-d) δ 7.89-7.85 (m, Ar, 2H), 7.33-7.27 (m, Ar, 18H), 7.16-7.14 (m, Ar, 2H), 7.11-7.09 (m, Ar, 2H), 5.53 (d, J= 9.22 Hz, H-1, 1H), 4.87 (d, J= 10.9 Hz, H-6, 1H), 4.89 (d, J= 11.0 Hz, H-6, 1H), 4.85-4.72 (m, CH_2^{Bn}, 3H), 4.58-4.54 (m, CH_2^{Bn}, 1H), 4.51-4.46 (m, CH_2^{Bn}, 2H), 4.43-4.35 (m, H-3, 1H), 4.32-4.30 (m, CH_2^{Bn}, 1H), 3.89-3.87 (m, CH_2^{Bn}, 1H), 3.75 (t, J= 8.95, H-2, 1H), 3.71-3.67 (m, H-4, CH_2, 3H), 3.61-3.57 (m, H-5, CH_2, 3H), 2.73 (bs, OH, 1H), 2.37 (s, CH_3, 3H) ppm. ^{13}C NMR (126 MHz, Chloroform-d) δ 144.68, 138.4 5, 138.12, 137.92, 137.67, 129.44, 128.60, 128.58, 128.56, 128.50, 128.47, 128.32, 127.99, 127.93, 127.86, 86.77 (C-2), 85.86 (C-1), 77.160 (C-3, C-4, C-5 with Chloroform), 75.94, 75.20, 74.57, 73.50, 68.90, 68.32, 60.52, 21.77 ppm. HRMS (MALDI+): Calculated for $C_{44}H_{47}NO_{10}SNa^+$ m/z 804.28129; found m/z 804.27668. $[\alpha]_D^{298}$= -1,65.

2,3,4,6-Tetra-O-benzyl -D-glucopyranosyl oxy-ethyl tosylcarbamate (31a)

The product was obtained as a α/β mixture (2:3) and isolated as a colorless oil (R_f = 0.23, PE:AcOEt 1:1+2% of MeOH) . ^{1}H NMR (500 MHz, Chloroform-d) δ 8.72 (s, NH, 1H), 7.94 (m, Ar, 2H), 7.90-7.87 (m, Ar, 2H), 7.84-7.82 (m, Ar, 1H), 7.36-7.27 (m, Ar, 44H), 7.20-7.12 (m, Ar, 4H), 4.98 (dd, J= 10.9, 4.45 Hz, CH, 1H), 4.92 (dd, J= 10.9, 4.42 Hz, CH, 1H), 4.87-4.76 (m, 6H), 4.71-4.55 (m, H-1α, CH_2^{Bn},7H), 4.53-4.46 (m, 2H), 4.33 (d, J= 7.91 Hz, H-1β, 1H), 4.30-4.27 (m, 2H), 4.25-4.20 (m, 2H), 4.03-3.90 (m, H-6β, H-3α, H-5α, 3H), 3.80 (m, H-6β, 1H), 3.79-3.71 (m, 4H), 3.67-3.50 (m, H-2α, H-3β, H-6α, CH_2, 5H), 3.45-3.33 (m, H-4β, H-2β, H-4α, 3H), 2.40 (s, CH_3, 3H), 2.39 (s, CH_3, 3H) ppm. ^{13}C NMR (126 MHz, Chloroform-d) δ 150.68 (C=O), 150.62 (C=O), 145.03, 144.88, 138.79, 138.61, 138.58, 138.20, 138.05, 137.94, 137.85, 137.63, 137.76, 135.71, 129.84, 129.71, 129.63, 128.66, 128.59, 128.57, 128.55, 128.52, 128.51, 128.47, 128.23, 128.20, 128.19, 128.12, 128.11, 128.05, 128.04, 128.01, 127.97, 127.94, 127.80, 104.08 (C-1β), 97.73 (C-1α), 84.65 (C-2α), 82.23 (C-2β), 81.87 (C-5α), 80.02 (C-3β), 78.19 (C-4α), 77.81 (C-5β), 75.88, 75.83, 75.36, 75.15, 74.81, 74.71 (C-4β), 73.65, 73.62, 73.51, 70.72 (C-3α), 69.71 (C-6α), 68.91, 67.93 (C-

6β), 66.63, 65.69, 65.45, 21.78 ppm. HRMS (MALDI+): Calculated for $C_{44}H_{47}NO_{10}SNa^+$ m/z 804.28129; found m/z 804.28935. $[\alpha]_D^{298}$= +12.7.

Synthesis of Ethyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (136)



Procedure K: EtOH (13 µL, 0.223 mmol) was added to a solution of trichloroacetimidate (100 mg, 0.146 mmol) and TfOLi (4 mg, 20% mol) in dry DCM. The reaction mixture was stirred at RT for 48h. The solvent was removed and the crude product was purified through chromatographic column (EPT: AcOEt 8:1) to yield the α-anomer (**136a**) as a colorless oil (24 mg, 0.043 mmol, 29 %), β-anomer (**136b**) as a colorless oil (24 mg, 0.043 mmol, 20 %) and product **129** (2 mg, 0.0036 mmol, 2 %). ^{1}H-NMR was in accordance with the literature.[73,100]

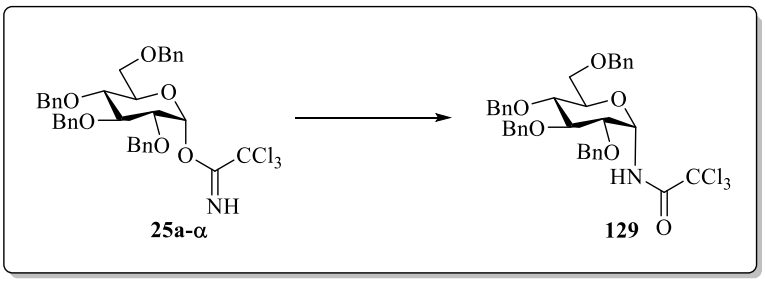
Procedure L: EtOH (13 µL, 0.223 mmol) was added to a solution of trichloroacetimidate (100 mg, 0.146 mmol) and Tf_2NLi (8 mg, 20% mol) in dry DCM. The reaction mixture was stirred at RT for 48h. The solvent was removed with any purification of the crude product (60 mg, yellow oil).

TABLE F: Using EtOH as acceptor

Entry	*Procedure*	*Trichloroacetimidate (25a-α)*	*EtOH*	*Solvent*	*T (°C)*	*136a:136b**
1	**K**	0.073 M (1.0 eq.)	0.111 M (1.5 eq.)	DCM	RT	56:44
2	**L**	0.073 M (1.0 eq.)	0.111 M (1.5 eq.)	DCM	RT	25:75

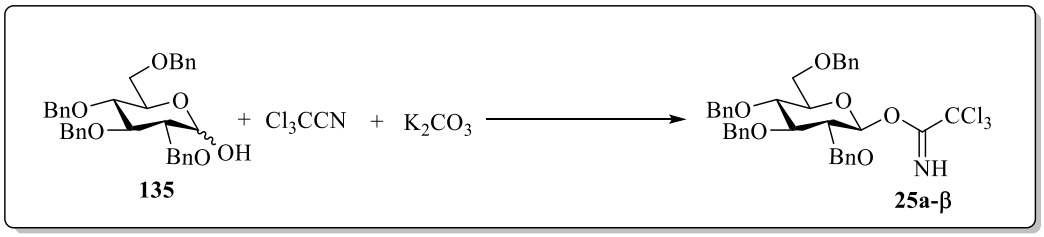
*The data reported were determined through ^{1}H-NMR of the crude product.

Synthesis of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (129)



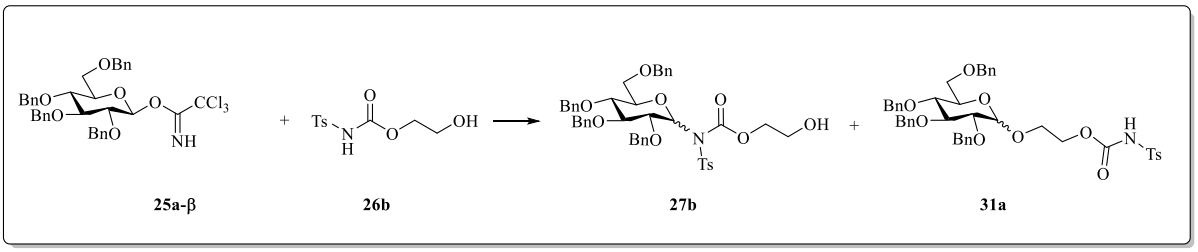
A mixture of 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) and TfOLi (4 mg, 20% mol) in dry DCM was stirred at RT for 48h. The solvent was removed without any purification of the obtained red oil (115 mg). NMR data of the crude product were consistent with the reported in literature.

Synthesis of 2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl trichloroacetimidate (25a-β)



K_2CO_3 (2.05 g, 14,8 mmol), trichloroacetonitrile (1.9 mL, 18.9 mmol) were added to a solution of 2,3,4,6-tetra-O-benzyl-D-glucopyranose (2 g, 3,70 mmol) in dry DCM (12 mL). The reaction mixture was stirred for 3 h at RT and evaporated under vacuo onto celite. The crude product was purified through chromatographic column (EPT: AcOEt 9:1 →7:1 + 0,5% of Et_3N) to yield the desired product (2.29 g, 3.34 mmol, 90 %) as a mixture of anomers from which fractions containing primarily the β-anomer could be isolated (623 mg, 909 mmol). NMR of the mixed fractions showed α/β 30:60. From this data it was possible to determinate the yield of the desired product (1.52 g, 2.22 mmol, 60%). NMR data of the compound **25a-β** were consistent with the reported in literature.[101] β-anomer: ^{1}H NMR (500 MHz, Chloroform-d) δ 8.71 (s, NH, 1H), 7.33-7.27 (m, Ar, 20H), 7.18-7.17 (m, Ar, 2H), 5.81 (m, H-1, 1H), 4.95 (d, CH_2, J=10.8 Hz, 1H), 4.91 (d, CH_2, J=11.0 Hz, 1H), 4.82 (m, CH_2, 2H), 4.76 (d, CH_2, J=10.9 Hz, 1H), 4.62 (d, CH_2, J=12.2 Hz, 1H), 4.58 (d, CH_2, J=10.9 Hz, 1H), 4.55 (d, CH_2, J=12.2 Hz, 1H), 3.78-3.72 (m, H-2, H-3, H-4, 4H) 3.65 (m, H-6, 1H).

Synthesis of 2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl 2-hydroxyethyl tosylcarbamate (27b) and **2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl oxy-ethyl tosylcarbamate (31a)**



2-hydroxyethyl tosylcarbamate (57 mg, 0.220 mmol) was added to a vial containing a solution of 2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl trichloroacetimidate (100 mg, 0.146 mmol) in dry DCM (2 mL). The reaction mixture was stirred for 48h. Then, it was extracted with NaOH 1M, washed with NH_4Cl, Brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to obtain the crude product as yellow oil. It was purified through chromatographic column (EPT: AcOEt 2:1). The desired product (colorless oil, 37 mg, 0.047 mmol, 33%) was obtained as a mixture of O-glycoside (α/β 3:1) and N-glycoside (α/β 7:3) in a 40:60 ratio. ^{1}H NMR (500 MHz, Chloroform-d) δ 8.66 (s, NH, 1H), 7.89-7.82 (m, Ar, 6H), 7.36-7.27 (m, Ar, 52H), 7.25-7.06 (m, Ar, 15H), 6.43 (d, J= 7.95 Hz, H-1α (41), 1H), 5.53 (d, J= 9.25 Hz, H-1β (41), 1H), 4.98-4.75 (m, H-6β (41), CH_2^{Bn}, 12H), 4.74-4.54 (m, H-1α (42), CH_2^{Bn}, 12H), 4.52-4.44 (m, H-3α (41), CH_2^{Bn}, 4H), 4.42-4.36 (m, H-3β (41), CH_2^{Bn}, 1H), 4.32-4.27 (m, H-1β (42), CH_2^{Bn}, 1H), 4.23-4.16 (m, H-5α (41), CH_2^{Bn}, 4H), 4.15-4.09 (m, H-2α (41), CH_2^{Bn}, 4H), 3.99-3.90 (m, H-6β (42), H-3α (42), H-5α (42), 3H), 3.79-3.69 (m, H-6α (41), H-2β (41), H-4β (41), H-6β (42), CH_2^{Bn}, 7H), 3.64-3.49 (m, H-4α (41), H-6α (41), H-5β (41), H-2α (42), H-3β (42), H-6α (4), CH_2 (42), 10H), 3.45-3.32 (m, H-4β (42), H-2β (42), H-4α (42), 2H), 2.39 (s, CH_3 (42), 3H), 2.37 (s, CH_3 (41β), 2H), 2.33 (s, CH_3 (41α), 3H). ^{13}C NMR (126 MHz, Chloroform-d) δ 152.88 (C=O), 150.64 (C=O), 144.86, 144.74, 138.78, 138.76, 138.26, 138.20, 138.14, 137.97, 137.61, 136.96, 136.68, 129.62, 129.42, 128.65, 128.53, 128.51, 128.49, 128.46, 128.45, 128.26, 128.23, 128.19, 128.10, 128.03, 127.98, 127.92, 127.84, 127.81, 127.79, 127.71, 104.09 (C-1β (42)), 97.80 (C-1α (42)), 86.74 (C-2β (41)), 85.83 (C-1β (41)), 84.65 (C-2α (41)), 82.48 (C-3α (41)), 82.21 (C-2β (42)), 81.88 (C-5α (42)), 81.81 (C-1α (41)), 80.01 (C-3β (42)), 79.05 (C-2α (41)), 78.19 (C-4α (42)), 77.92, 77.160 (C-3β (41), C-4β (41), C-5β (41), C-4α (41), C-6α (41) with Chloroform), 75.87, 75.32, 75.17, 74.84, 74.58 74.31 (C-5α (41)), 73.85, 73.78, 73.64, 73.60, 73.47, 70.76 (C-3α (42)), 69.87, 69.77 (C-6α (42)), 69.48, 66.75, 65.47, 60.48, 60.34, 21.76, 21.74, 21.69.

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